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MELENA NEONATORUM

AN EXPERIMENTAL STUDY OF THE EFFECT OF THE ORAL ADMINISTRATION OF BLOOD ON THE STOOLS

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OBSTETRICIANS and pediatricians have contended for many years that grossly bloody stools passed by a newborn infant in the first or second day of life might be the result of the ingestion of maternal blood during the labor period. This hypothesis emanates from clinical observations which were reported in the German literature around the turn of the century.

The present project was undertaken to determine whether blood introduced into the stomach of a newborn infant could produce grossly bloody stools. When it became evident that this could be accomplished, additional studies were performed in a group of newborn infants to determine the time of appearance and duration of grossly bloody stools and a positive test for occult blood after the intragastric administration of blood. For comparison, a similar study was carried out in older newborn infants who had evacuated their meconium.

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MATERIALS AND METHODS

Measured amounts of blood, taken from adults or the cords of newborn infants, were given by gavage to normal infants within several hours after birth. The deliveries were uncomplicated. The blood was collected in bottles containing either dry oxalate salts or anticoagulant acid citrate dextrose Solution A (1.2 ml. for each 10 ml. of blood). The amount of whole blood administered, exclusive of the volume of anticoagulant, was used in the data to be presented. A piece of polyethylene tubing was passed into the stomach and the contents removed to be certain that no blood was present. The blood was instilled at the rate of 1 ml. a minute, or more rapidly if the infant consumed it without becoming nauseated. Only the infants who retained the amount of blood given were included in the study. No fluids were given by mouth for twenty-four to thirty-six hours—the usual practice in the newborn nursery.

All stools were examined shortly after they were passed. The gross ap-

pearance was noted and the guaiac test for the presence of blood was performed.

To compare the effect of blood given by gavage on the stools after meconium had been passed, measured amounts of blood were given to infants 3 or 4 days of age. Before the blood was administered, tests for occult blood were performed on at least two stools which had been passed consecutively, to make certain that none was present. Many of the older infants had been subjects in the first part of the study. The blood was given in place of one feeding and the regular feeding schedule was then continued. All stools were examined for gross and occult blood.

To determine the incidence of occult blood in the stools of normal newborn infants, the guaiac test was performed on all stools passed by thirty-five infants during their five-day hospital stay. Delivery had been spontaneous and the labor uncomplicated. The chemical test was negative in all instances. The results of this study were not in agreement with the observations made by Bonar[1] in 1928. He reported that "in only eight of 109 infants the stools did not show any occult blood" throughout a ten-day hospitalization. Bonar used the benzidine test. Although many workers are of the opinion that the benzidine test is more sensitive than the guaiac test, Bonar found that the two tests agreed closely in this experience. Admittedly, obstetrical management and care of the newborn infant may not have been as favorable as it is at the present time.

TABLE I. EFFECT OF INTRAGASTRIC ADMINISTRATION OF BLOOD ON THE STOOLS OF NEWBORN INFANTS

AMOUNT OF BLOOD (ML.)	NO. OF INFANTS RECEIVING BLOOD	GROSSLY BLOODY STOOLS				OCCULT BLOOD IN STOOLS		
		NO. OF INFANTS	FIRST NOTED (RANGE)*	DURATION (RANGE)*	NO. OF STOOLS (RANGE)	FIRST NOTED (RANGE)*	DURATION (RANGE)*	NO. OF STOOLS (RANGE)
A. During Meconium Period								
40	3	3	10-20	14-28	4-7	10-17	34-64	9-12
35	5	4	9-15	20-37	4-9	7-12	20-49	6-9
30	15	8	9-30	12-45	2-7	8-48	21-87	3-10
25	3	2	15-18	-40	1-6	14-16	47-61	5-9
20	7	2	17-18	32-40	4-6	7-23	21-70	4-14
15	8	2	19-30	14-	1-3	9-30	17-45	3-10
B. After Meconium Period								
20	5	5	3-12	3-15	2-5	3-4	18-26	3-7
15	5	5	2.5-10	1.5-14	1-4	2.5-10	7-46	3-8
10	10	10	3.5-10	1-9	2-3	3.5-10	10-31	3-8

*Hours.

RESULTS

A summary of the results of the effect of the intragastric administration of blood on the stools of newborn infants is given in Tables I and II.

Grossly bloody stools could be produced by instilling blood into the infant's stomach within several hours after birth. The success with which one could produce bloody stools seemed to be related directly to the amount of blood administered. Whereas two of the eight infants passed grossly bloody stools when

TABLE II. CONDENSATION OF THE DATA PRESENTED IN TABLE I (SEE TEXT)

AMOUNT OF BLOOD GIVEN (ML.)	GROSSLY BLOODY STOOLS							OCCULT BLOOD IN STOOLS						
	NO. OF OBSERVATIONS	FIRST NOTED (HR.)		DURATION (HR.)		NO. OF STOOLS		NO. OF OBSERVATIONS	FIRST NOTED (HR.)		DURATION (HR.)		NO. OF STOOLS	
		M*	Md†	M	Md	M	Md		M	Md	M	Md	M	Md
A. During Meconium Period														
35-40	7	12	10	24	21	6	6	8	11	10	34	37	8	8
25-30	10	17	15	30	34	4	4	10	17	15	30	34	4	4
15-20	4	21	18	29	32	3	3	15	18	17	40	39	7	6
B. After Meconium Period														
20	5	5	4	10	10	3	4	5	4	4	21	22	5	5
15	5	7	7	7	6	2	2	5	7	7	25	26	5	5
10	10	8	7	5	5	2	2	10	7	7	17	15	4	3

*M, Mean.
†Md, Median.

given 15 ml. of blood, seven of the eight infants had bloody stools when given 35 to 40 ml. of blood. The guaiac test was positive after all doses of blood were given even though gross blood was only seen in some cases.

In contrast, all ten infants given as little as 10 ml. of blood after meconium had been evacuated passed grossly bloody stools. The difference in the effect of blood on the stools during and after the meconium period probably is related to gastrointestinal motility and the presence of bulky, sticky, viscid meconium.

The number of infants in each group given a measured amount of blood was too small to draw definite conclusions as to the relationship between the amount of blood given and the time of appearance, duration and number of grossly bloody stools, either before or after the meconium period. The same was true of stools containing occult blood. In Table I, the overlap in the range of the observations is demonstrated. There was a continuous distribution of the values within the ranges cited.

Only the suggestive trends can be pointed out from the summary of the data in Table II. During the meconium period, grossly bloody stools and occult blood in the stools appeared sooner when larger amounts of blood were given. No conclusions can be drawn from similar observations after meconium had been evacuated, because of the small difference in the amounts of blood given. However, infants given 20 ml. of blood had bloody stools earlier than those given less than this amount. Grossly bloody stools were passed earlier after the meconium stage, even though smaller amounts of blood had been given than during the meconium period.

Infants given 35 to 40 ml. of blood passed a larger number of bloody meconium stools, yet over a shorter period of time, than those given smaller amounts of blood. However, after the meconium had been passed, bloody stools persisted longer, and there were more stools when larger amounts of blood were given.

During the meconium period, there was no clear-cut trend in either the span of time during which stools with occult blood were passed or in the number of stools containing occult blood after amounts of blood varying from 15 to 40 ml. were given. As expected, blood was evacuated from the bowel more quickly after the meconium period than during the period when meconium was still in the intestinal tract.

SUMMARY AND CONCLUSIONS

Measured amounts of blood (15 to 40 ml.) were given as a single instillation by gavage to infants within several hours after birth. A relatively large amount of blood (35 to 40 ml.) was necessary to produce grossly bloody stools in the majority of infants. The grossly bloody stools were noted as early as nine hours and as late as thirty hours after the introduction of blood into the stomach. Grossly bloody stools were passed for twelve to forty-five hours. Occult blood (guaiac test) was detected in stools within seven hours and was present for as long as eighty-seven hours after blood had been given.

A similar study was made in older newborn infants who had evacuated their meconium. The amount of blood

given was 10 to 20 ml. Much less blood (10 ml.) produced grossly bloody stools. Both grossly bloody stools and occult blood appeared as early as two and one-half hours after the administration of blood. The passage of grossly bloody stools continued for as long as fifteen hours. A positive guaiac test for occult blood persisted for a period up to forty-six hours.

The guaiac test for occult blood was performed on all the stools passed by thirty-five normal newborn infants during their five-day hospitalization. In all instances the test was negative.

Although the number of infants in the study was too small to enable one to draw definite conclusions, because of the lack of available information on the subject, it seemed worth while to report the data. The results may be of help to the clinician who may assume that the persistence of grossly bloody stools and a positive chemical test for blood indicate that there is continuing hemorrhage into the digestive tract of a newborn infant. Evidence has been presented that this may not be true.

I wish to express my appreciation to the Beth Israel Hospital, Boston, and the Boston City Hospital for allowing the study to be carried out in their nurseries, and to the nursing staff for their assistance and cooperation.

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"MELENA" NEONATORUM: THE SWALLOWED BLOOD SYNDROME

A Simple Test for the Differentiation of Adult and Fetal Hemoglobin in Bloody Stools

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EXPERIMENTAL studies were undertaken previously[1] in an attempt to shed some light on the supposition that grossly bloody stools may be passed by a newborn infant as a result of swallowing maternal blood during the labor period. When it became evident that the instillation of large amounts of blood into the stomach of a newborn infant may produce grossly bloody stools, a simple, rapid bedside test was devised to enable one to distinguish between maternal and infant's blood in the stool. Prompt identification of adult type of hemoglobin, presumably swallowed maternal blood, would spare the newborn infant from having to undergo unnecessary blood tests, radiographic examinations, and perhaps surgical exploration. The practicality of the test was proved when used in a series of patients with "melena" neonatorum.

Unfortunately the word melena is used by many physicians in a general sense to denote bloody stools or blood in the stools, rather than black stools which was its original meaning. Since the circumstances in this paper deal mainly with stools which are grossly bloody with varied shades of red, we have avoided the use of the word melena. This distinction of terms is purposeful because the test mentioned above is of no value when used on a tarry stool.

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MATERIALS AND METHODS

The test used to distinguish between maternal and infant's blood is based on the fact that the hemoglobin in an adult differs from the predominant type of hemoglobin in the blood of the fetus and newborn infant in its reaction with alkali. Von Körber[2] in 1866 and von Krüger[3] in 1887 demonstrated that hemoglobin solutions prepared from human placental blood show a greater resistance to denaturation with alkaline reagents than do specimens obtained from the blood of normal adults. The pink hemoglobin solution prepared from an adult's blood is changed to a brown-yellow in one to two minutes after the addition of an alkali because of the conversion of oxyhemoglobin to alkaline globin hematin. The color change is readily seen; no instruments are needed. The hemoglobin of the newborn infant, which consists mostly of fetal pigment, is more resistant to denaturation with alkali. The pink hemoglobin solution, therefore, persists in this two-minute interval. The presence of a small amount of adult type

of hemoglobin in the newborn infant's blood does not appreciably complicate the interpretation of the color change, for the hemoglobin solution remains predominantly pink after the addition of alkali.

The technique of the test used on the bloody stools is as follows. A small amount of stool is mixed with water (tap or distilled) in a test tube to lyse the erythrocytes and to prepare a hemoglobin solution. The proportion of stool to water used is variable and depends on the blood content of the stool. Usually one part of stool to five or ten parts of water is the initial proportion. A distinct pink supernatant solution is required to see clearly the color change that may take place after the addition of alkali. *It is important that the stool be grossly bloody (red) and not tarry, for in a tarry stool the oxyhemoglobin has already been converted to hematin.* The test tube is centrifuged for one to two minutes at 2,000 r.p.m. to separate the fecal matter. The supernatant hemoglobin solution is then filtered or decanted. Approximately 1 ml. of 0.25 normal (1 per cent) sodium hydroxide is mixed with approximately 5 ml. of the hemoglobin solution to be tested. The color change is read after two minutes. If the hemoglobin is of the adult type, the solution changes from pink to brown-yellow. The fetal hemoglobin solution of infant's blood remains predominantly pink. To estimate the degree of color change, if any, attributable to the presence of adult type of hemoglobin in the newborn infant's blood, a control test is performed simultaneously, using the peripheral blood of the infant who passed the bloody stool.

To establish the validity of the test, six infants were given sufficient blood by gavage to produce grossly bloody stools. Cord blood was given to three, and adult blood was administered to the others. The two types of hemoglobin in the stools were identified correctly by the described technique.

When only a blood-stained diaper is available, the test can be modified by adding the water and sodium hydroxide directly to the stain. The specific type of hemoglobin pigment is detectable by this method.

A more sensitive method[4] may prove to be advantageous in some cases.

Spectrophotometry is a more precise method of distinguishing between the two types of hemoglobin. The method was used as a confirmatory procedure at the start of the study but in most instances thereafter it was not necessary.

CASE REPORTS

The first seven case presentations, summarized in Table I, are those in which swallowed maternal blood was regarded as the source of the blood in the grossly bloody stools. The hemoglobin-alkali test performed on the bloody stools was positive for adult hemoglobin.

The important clinical features of six infants with bloody stools caused by intrinsic hemorrhage are outlined in Table II. It was shown by use of the hemoglobin-alkali test that the hemoglobin in the bloody stools was of the fetal type.

DISCUSSION

The alkali denaturation test performed on the hemoglobin in a grossly

bloody stool was useful in distinguishing between the patients with grossly bloody stools produced by intrinsic hemorrhage and those with bloody stools caused by the swallowing of maternal blood. Early diagnosis and appropriate therapy could thus be facilitated. When the result of the test indicated that the hemoglobin was of the adult type, the infant's clinical status was cautiously observed and a minimum of laboratory tests were

TABLE I. BLOODY STOOLS CAUSED BY SWALLOWED MATERNAL BLOOD (HEMOGLOBIN-ALKALI TEST: POSITIVE FOR ADULT HEMOGLOBIN)

PATIENT	BLOODY STOOLS: FIRST NOTED (HR. AFTER BIRTH)	BLOODY STOOLS: DURATION (HR.)	BLOODY STOOLS: NO. OF STOOLS	BLOOD STUDIES: INITIAL		BLOOD STUDIES: DISCHARGE	BLEEDING TIME CLOTTING TIME* PROTHROMBIN TIME†	COMPLICATIONS OF LABOR
1 B. B. M.	5	48	6	Hb. Ht. Retic	12.5 39.0 2.3	12.2 39.0 0.7	Normal	Vaginal bleeding and labor: 2½ hr. Premature separation of placenta Bloody amniotic fluid
2 N. F.	5 min.	52	17	Hb. RBC	13.5 4.09	12.4 4.16	Normal	Vaginal bleeding 5 hr. before delivery Premature separation of placenta Cesarean section Bloody amniotic fluid
3 B. B. W.	9	21	4	Hb. Ht.	16.1 58.0	15.3 58.0	Normal	Vaginal staining 1 day before delivery Labor: 2 hr. Premature separation of placenta Bloody amniotic fluid
4 B. B. S.	7.5	64	12	Hb. RBC	12.0 3.67	13.3 4.04	Normal	Vaginal staining 4 hr. before induction of labor Premature separation placenta Rupture of membranes —labor Labor: 10 hr. Bloody amniotic fluid
5 B. B. B.	5 min.	26	7	Hb. RBC	18.3 5.49	16.4 5.08	Normal	Spontaneous rupture membranes—bleeding and labor: 2 hr. before delivery Premature separation of placenta Cesarean section
6 M. C.	7	48	?	Hb. RBC	16.0 5.3	16.0	Normal	Vaginal bleeding 14 hr. before delivery Labor: 11 hr. Premature separation of placenta Cesarean section
7 B. G. P.	4.5	21.5	9	Hb.	16.0	14.5	Normal	Vaginal bleeding for 7 da. before delivery Premature separation of placenta Cesarean section Bloody amniotic fluid

*Lee-White method.
†Quick's one-stage procedure.

performed. Thus the infant had little annoyance and discomfort. The presence of fetal hemoglobin, on the other hand, prompted the physician to search for an intrinsic cause of the bleeding—careful and repeated physical examinations, more elaborate blood studies, and radiographic examinations. Case 8 illustrates the latter situation. Even though the infant did not appear acutely ill on admission, the swallowing of maternal blood disclosed a consistent pattern with the following characteristics: (1) onset: grossly bloody stools passed within twelve hours after birth (minutes to nine hours after birth); (2) no anemia during hospitalization, or moderate anemia but no further appreciable decrease in the blood values; (3) bleeding, clotting, and prothrombin times normal; (4) complication of labor—vaginal bleeding resulting from a premature (marginal) separation of the placenta; the amniotic fluid was bloody in five cases; a cesarean section was performed on the mothers of four of the infants; and (5) clinical condition of the infant good throughout hospital stay in spite of what appeared to be considerable blood loss in the stools.

TABLE II. BLOODY STOOLS CAUSED BY INTRINSIC HEMORRHAGE (HEMOGLOBIN-ALKALI TEST: POSITIVE FOR FETAL HEMOGLOBIN)

PATIENT	DIAGNOSIS	COMPLICATIONS OF LABOR	BLOODY STOOLS FIRST NOTED (HR. AFTER BIRTH)	VOMITING (HR. AFTER BIRTH)	OBSERVED DECREASE HEMOGLOBIN CONCENTRATION (GM. %)	BLEEDING TIME CLOTTING TIME PROTHROMBIN TIME
8 M. H.	Volvulus—small bowel	None	36	"Several"	16.5 → 14.5	Normal
9 L. H.	Sepsis	Severe respiratory infection	72	72	13.0 → 13.0	Normal
10 B. B. K.	Sepsis Hepatitis	None	36	None	16.0 → 8.0	Bleeding time—increased
11 B. G. S.	Idiopathic "melena neonatorum"	Elective cesarean section—ovarian cyst	8	None	14.5 → 10.0	Normal
12 B. G. L.	Postmaturity, ? Esophageal or upper G.I. ulcer	None	29	24	18.0 → 11.4	Bleeding time—increased
13 B. G. G.	? Esophageal or upper G.I. ulcer	Elective cesarean section—previous cesarean section	34	34	11.8 → 9.0	Normal

was not anemic, and had no signs of intestinal obstruction, the presence of fetal hemoglobin in the bloody stool induced the admitting physician to observe the infant closely. This led to early diagnosis, surgical repair of a serious surgical condition in a newborn infant, and prompt recovery.

An analysis of the seven cases in which bloody stools were caused by

In contrast, the features of the six cases of grossly bloody stools resulting from intrinsic hemorrhage were: (1) Onset: bloody stools passed usually after one day of age (8, 29, 36, 36, 36, 72 hours after birth). (2) A significant decrease in hemoglobin concentration during the period of bloody stools. An anemia developed in all cases even though the hemoglobin concentration was normal on the initial determination. (3) Bleeding and coagulation tests more likely to be abnormal. The bleeding time was increased in two of the six infants (4 and 12 minutes); the coagulation time was at the upper limits of normal in one infant. The normal clotting and prothrombin times which were obtained at the time of admission to the hospital may have been influenced by vitamin K therapy given prior to the time of transfer. (4) No complications of labor characterized by vaginal bleeding. Two elective cesarean sections were performed —one because of a previous cesarean section, the other on account of obstruction from a large ovarian cyst. (5) Grossly bloody stools were merely one manifestation of the primary illness, i.e., sepsis, intestinal obstruction, (?) gastrointestinal ulcer, etc. The infants appeared ill—the clinical condition commensurate with the severity of the fundamental illness. Vomiting was more prominent in the clinical picture; four of the six infants had this symptom.

The presence of maternal blood in the amniotic fluid may be explained in the following manner. On occasion, when a marginal separation of the placenta takes place, rupture of the chorion laeve and amnion in the adjacent area may also occur. The chorionic plate in the region of the marginal sinus (maternal blood) is thin and thus dissection of the blood through the thin amnion into the amniotic fluid is feasible. This possibility is substantiated by the evidence, in cases of amniotic fluid embolism, of passage of amniotic fluid contents into maternal sinusoids at the placental margin.[5]

Offhand, one may wonder why three of the seven infants had a moderate anemia (hemoglobin concentrations 12.0, 12.5, 13.5 Gm. per 100 ml. blood) if the blood in the stool was supposedly from an extraneous source. Our explanation can only be speculative. With the premature separation of the placenta it is possible that there may be some bleeding from the fetal villi of the chorion. The fetal blood, however, probably promptly becomes mixed and well diluted with the blood in the maternal sinusoids. A portion of the mixed blood may pass into the amniotic sac, but more likely it drains into the maternal circulation. Nevertheless, even if part of the mixed blood should get into the amniotic sac, the quantity of blood flowing from a ruptured marginal sinus is so much larger than the amount coming from the peripheral sinusoids that the relative concentration of fetal hemoglobin would be so low as to preclude detection by the simple qualitative hemoglobin-alkali test. Perhaps this point can be more clearly defined by quantitative tests in future cases. Another factor which may have accounted in part for the infants' lowered hemoglobin concentrations was the early ligation of the umbilical cord by the obstetri-

cian in dealing with the complicated labors. However, whatever the precise explanation may be, the significant facts that seem to exclude intrinsic hemorrhage are (1) no appreciable further decrease in the hemoglobin concentrations during the period of grossly bloody stools and (2) hemoglobin in the stools of the adult type.

The suggestion that grossly bloody stools may be the result of aspiration of maternal blood in utero in cases of premature separation of the placenta was made many years ago. Observation of such cases were made by Hellweg,[6] Widerhofer,[7] Baisch,[8] and Kamann.[9]

Although the blood swallowed by the infants presented here was of maternal origin, it is possible to have blood in the amniotic fluid derived from the fetal circulation. This may occur if there is a tear in an umbilical vessel which passes through the amniotic sac wall (insertia velamentosa). Ebart[10] speculated on this possibility in 1723. Schicke[11] described a similar case. The amniotic fluid was bloody. The umbilical vessels were fanlike; one of the aberrant vessels was torn and crossed through the amniotic sac wall. There was no maternal trauma, abnormality of labor, or delivery. It is reasonable to suspect that in cases of this type the infant may have anemia at birth but no further decrease in blood values during the period of grossly bloody stools. In addition, the time of appearance of grossly bloody stools would probably be less than twelve hours after birth. These are two of the five characteristics found in the cases of grossly bloody stools caused by the swallowing of maternal blood.

SUMMARY

A simple qualitative test was devised to enable one to distinguish between maternal (adult type) and infant's (fetal type) hemoglobin in a grossly bloody stool. The test is based on the fact that fetal hemoglobin is more resistant to denaturation with alkali than adult hemoglobin. The validity of the test was confirmed by the successful differentiation of cord blood (predominantly fetal hemoglobin) and blood from adults, given by gavage, in the grossly bloody stools.

When the alkali denaturation test was used in thirteen cases in which newborn infants passed grossly bloody stools, there were seven who had hemoglobin in their stools of the adult type. It was assumed that these infants had swallowed maternal blood in utero. The benign clinical course was predicted and the infant spared from many blood tests, radiographic examinations, and perhaps surgical exploration.

The cases in which grossly bloody stools were caused by the swallowing of maternal blood had the following characteristics: (1) appearance of grossly bloody stools less than twelve hours after birth, (2) no anemia during hospitalization, or moderate anemia but no further appreciable decrease in blood values; (3) bleeding, clotting, and prothrombin times normal; (4) complication of labor—vaginal bleeding resulting from a premature (marginal) separation of the placenta; and (5) clinical condition of the infant good throughout the hospital stay in spite of what ap-

peared to be considerable blood loss in the stools.

The contrasting features of the cases in which intrinsic hemorrhage caused the bloody stools are given.

The rare instance whereby swallowed blood from bloody amniotic fluid may be solely of fetal origin is cited.

Further experience with this simple, qualitative hemoglobin-alkali test is needed to establish its precise value. It may be necessary to resort to more sensitive quantitative tests with future cases. The necessity did not arise in the seven cases described.

We gratefully acknowledge the contribution of cases to the series from the nurseries of the Beth Israel Hospital, Boston, and the Boston Lying-In Hospital.

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THE PROBLEM OF PREMATURITY

Obstetric, Pediatric, and Socioeconomic Factors

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THE premature infant, representing but a fraction of the total births, is responsible for over one-half of the deaths in the first twenty-eight days of life. Techniques designed to benefit the premature baby have been developed by obstetricians and pediatricians and made generally available by public health authorities. These efforts have contributed to the recent drop of 40 per cent in the neonatal mortality rate for the United States—a fall from 32.5 in 1935 to 20 per 1,000 live births in 1951. Experience in widely separated maternity hospitals has proved that a neonatal rate of 13 per 1,000 could be achieved by the country as a whole through the wide application of present "know-how." This would mean the saving of nearly 30,000 babies every year.

Current efforts in research centers to further lower neonatal mortality have run into a stalemate—apparently present methods have extracted all the "pay dirt" of which they are capable. Attention is now being focused on solution of the problem through the prevention of prematurity itself. *Accumulating evidence suggests that much of our past success may have been achieved through the fortuitous aid of a silent ally—improving socioeconomic conditions.* Intensive study of these forces is needed to discover what specific socioeconomic factors appear to influence premature birth.

THE OBSTETRIC PROBLEM

From the publications of Eastman,[1] Hellman,[2] Potter[3] and Bloch and associates,[4] the maternal complications associated with premature stillbirths and live births in 69,145 deliveries can be estimated. Between 60 and 70 per cent of the premature births were spontaneous from mothers with no known complication. From 8 to 13 per cent of the premature infants were twins. About 10 per cent were of mothers with toxemia, approximately 10 per cent were associated with maternal bleeding, while 4 per cent were in infants with malformations or erythroblastosis.

The obstetrician's dilemma is the 70 per cent of premature births that occur spontaneously in apparently normal mothers; this problem will be considered in the last section of this paper.

Multiple pregnancies terminate, on the average, three weeks before the expected date of confinement. Forewarned is forearmed, and the mother with twins requires special prenatal attention to physical health, nutri-

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tion, and rest. At delivery, the second twin runs the greater risk, the breech is frequently presenting, and anoxia may be operating; great skill and gentleness are required at this delivery.

Toxemia appears to be less severe than formerly; whether this is due to prenatal care, attention to diet, and salt restriction is not known. Certainly close prenatal attention is indicated; hospitalization at critical times may postpone the onset of labor. Several weeks in the hospital for the mother is much cheaper than two months in the nursery for the baby.

Real progress has been made in the management of the bleeding patient in so far as the infant's welfare is concerned. With the universal availability of blood blanks, the former immediate delivery of the bleeding patient as an emergency has given way to the conservative treatment. To deliver a premature infant at the height of the hemorrhage makes him combat the shock and anoxia resulting from the placental hemorrhage at the same time he must face the hazards involved in any type of delivery. Even a few hours' delay, always assuming that the mother's condition permits, will get the fetus over the shock period and the infant in much better condition on delivery. In many instances the conservative treatment will allow added weeks for the fetus to mature; every week means 4 to 8 ounces, with each 8 ounce gain, the expected premature mortality is cut in half. Hellman[2] reports that the fetal loss rate by this procedure has been cut perhaps by 50 per cent, while Litchfield and associates[5] have reported a reduction in fetal mortality from 24 to 5 per cent.

Except in very rare circumstances, and then only after adequate consultation, pregnancy should never be prematurely terminated because of suspected erythroblastosis in the fetus.

About 10 per cent of our deaths in the first days of life showed evidence of intrauterine infection. Potter[6] states that bacteria are generally present in the amniotic fluid within six hours of the onset of labor even though the membranes are intact. Hertig[7] states that evidence of amnionitis and chorionitis can usually be found within eight hours of rupture of the membranes. Judd[8] offers no criticism to the use of antibiotics for fetal protection in patients with membranes ruptured for a period of twelve hours or longer, in febrile patients, or perhaps in the patient who is in labor for a long period of time. It must be borne in mind that the bacteria most often responsible for infection in the fetus and newborn infant are *Escherichia coli* and *Staphylococcus aureus;* therefore prophylactic therapy must include coverage for both gram-positive and gram-negative organisms.

A minimum of analgesia, or none at all, should be used prior to the birth of a premature infant. The use of morphine is definitely contraindicated. Taylor[9] believes that premature deliveries either from below or by cesarean section should be performed, using regional or local anesthesia; using this method he reports the 1,000 to 2,500 gram mortality rate to be an excellent 8.8 per cent at the University of Colorado. The use of spinal and caudal anesthesia demands the service of a skilled anesthetist—they are not without serious danger to the mother and infant. If a specially

qualified physician anesthetist were not available I would feel safer if the cesarean section were performed under general ether anesthesia. Under no circumstances should cyclopropane be used because of the fetal anoxia it produces.

In our experience the safest way to deliver a premature infant is from below, accompanied by a wide episiotomy and outlet forceps. Delivery by breech extraction carries the highest mortality and requires the utmost in obstetric judgment and skill.

Although the point is not definitely settled, the cord should be allowed to stop pulsating before it is clamped and cut. There is some evidence[8] that oxygen given to the mother by means of a mask capable of delivering 50 per cent oxygen, during labor and while cord pulsations continue, may combat fetal anoxia.

At the Boston Lying-in Hospital conservative methods of resuscitation are advocated. Fluid is drained from the bronchial tree by gravity with gentle postpharyngeal suction, rarely with tracheal suction, using a catheter. Oxygen is supplied under controlled positive pressure of not over 15 cm. of water through a tight-fitting mask. The stomach is then aspirated of liquid contents. We have no faith in "stimulants" and use no mechanical gadgets.

THE PEDIATRIC PROBLEM

It is the pediatric responsibility to see that the premature infant who survives the immediate postnatal period also survives the hazards of the neonatal period. This means that the nursery must be organized for the long-term care of these vulnerable babies. Detailed standards and regulations[10] for the hospital care of the premature infant are available, and every hospital, large or small, should abide by them.

The causes of neonatal mortality are the same as for mature infants and can be grouped into five positive categories.[10]

1. Postnatal asphyxia and atelectasis.
   a. Abnormal pulmonary ventilation.
   b. Anoxia.
   c. Hyaline pulmonary membrane.
2. Injury at birth.
3. Congenital malformations.
4. Infection.
5. Blood dyserasias.
   a. Hemolytic disease (erythroblastosis).
   b. Hemorrhagic disease.

POSTNATAL ASPHYXIA AND ATELECTASIS

Potter[6] has shown that it is not until the gestational age of 28 weeks and weight of 1,000 grams that enough capillaries have penetrated the oxygen barrier of cuboidal cells lining the pulmonary tree to make oxygenation and continued life a possibility. This condition is an important cause of "abnormal pulmonary ventilation." The borderline infant must be given every chance to demonstrate his ability to survive through treatment in an atmosphere of 50 to 60 per cent moist oxygen.

Anoxia produces a chain of events affecting every part of the body to varying degree and depending on the degree and duration of the insult. These events are congestion, edema, hemorrhage, and death of tissue. The clinical symptoms and their treatment depend on the organs involved. Frequently associated with anoxia, the smaller premature infants are par-

ticularly prone to develop an intraventricular hemorrhage originating from the choroid plexus or vena terminalis of the lateral ventricles. These infants may do well for two or three days, then develop spells of profound apnea and die; no treatment is known.

In about 60 per cent of the premature infants, and 20 per cent of the full-term infants, that die between the ages of 4 hours and 4 days, a varying amount of eosinophilic hyaline membrane is found lining the alveolar and alveolar ducts. Occasionally this membrane is found alone, but most frequently other serious pathologic lesions may also be present in the lungs or other vital areas of the body. The frequent finding of this membrane has resulted in the current vogue of calling "hyaline membrane disease" the most common cause of death in the newborn infant. In our clinical experience 70 to 80 per cent of the children with this severe respiratory distress syndrome recover. Recent x-ray studies by Peterson and Pendleton[11] from this clinic demonstrate a typical picture of a fine granular pattern in the lungs that is believed to be characteristic of the hyaline membrane syndrome. I have recently reviewed our material and am convinced that when the "hyaline membrane" babies die, it is not primarily because of the membrane but from associated conditions such as infection and hemorrhage. Since, although very distressed, most of the babies recover promptly by the fourth or fifth day, it is difficult to evaluate treatments. Certainly they need oxygen as they are cyanotic without it; it is customary to give water vapor in a fine mist, but its value has not been demonstrated. Silverman and Anderson[12] have recently demonstrated that wetting agents have no influence on this condition. Antibiotics should be given.

INJURY AT BIRTH

Intracranial hemorrhage, the result of birth trauma, has practically disappeared from modern obstetric hospitals. If more than a rare instance occurs, it is an indication that methods of obstetric management should be made the subject of critical review.

Subarachnoid hemorrhages are usually the result of intrauterine anoxia. Advocates for and against treatment by repeated drainage by lumbar puncture will be found. It is our policy to perform frequent lumbar punctures and continue treatments until the fluid is normal. I think more infants recover, and do so without hydrocephalus developing, than if expectant treatment is performed. Subdural hematomas are not infrequent in the newborn period, and it is very important in preventing later complications to make the diagnosis early. The symptoms may be convulsions, increased anterior fontanel pressure, lethargy, vomiting, failure to gain weight, and rapid increase in head size. The diagnosis is made by subdural punctures in conjunction with lumbar puncture. The treatment is repeated tapping and probably exploration and removal of part of the membrane. All suspected cases should have neurosurgical consultations.

CONGENITAL MALFORMATIONS

Infants with tracheoesophageal fistula are noted to pass excessive amounts of mucus from the moment of birth. This is enough on which to

suspect the diagnosis, and by passing a catheter and finding that it ends in a blind esophageal pouch the diagnosis can be made. Early diagnosis and surgery have converted this once fatal anomaly into one with a good prognosis.

Obstruction of the second portion of the duodenum is intrinsic or secondary to malrotation of the cecum. The diagnosis is suspected when the newborn vomits persistently from birth. A flat x-ray plate of the abdomen without the need of a contrasting meal will show the large, dilated stomach and first portion of the duodenum. Immediate surgery converts this once fatal condition into one with a good prognosis.

Diaphragmatic hernia occurs in the premature as in the full-term infant; the symptoms are cyanosis, dyspnea or vomiting; the diagnosis is made by x-ray and immediate surgery is indicated.

We have encountered annular pancreas, pyloric stenosis, intussusception, omphalocele, and inguinal hernia, all treated surgically. Gross[13] reports major surgery on 159 premature infants with a mortality rate of 45 per cent.

INFECTIONS

It has been the general contention that the death of any infant from infection, after having survived the first week of life in good condition, must be considered a preventable death until proved otherwise. Epidemic diarrhea of the newborn is an example of one highly fatal condition than can be either prevented or controlled by the strict practice of approved nursery technique. The premature infants, owing to their natural susceptibility and to their prolonged hospital stay, are particularly prone to infection. This is especially true in nurseries where premature infants are admitted after being born outside. We have had actual demonstration in the premature nursery of the Children's Hospital of how the needless loss of life from late infection can be brought under control. All of the premature infants cared for in this nursery were delivered outside our hospital and admitted for care and treatment. Between 1944 and 1947 there were 508 premature infants admitted, with a mortality of 50 per cent (see Table I). Thirty-two per cent of the deaths took place after one week of age, and autopsy showed 85 per cent of these deaths due to infection.

A program attempting to control this late infection problem was completed in late 1947. This plan included: (1) reconstruction of the nursery, isolating it and protecting it from contact with the rest of the hospital by as many barriers as possible, (2) terminal sterilization of all formulas and fluid for oral administration either by flowing steam or by steam under pressure, (3) a nursing and medical staff who dealt exclusively with the premature infants, (4) individual isolation of each infant from admission until ready for discharge, in an Isolette, and (5) prophylactic administration of 50,000 units of aqueous penicillin intramuscularly every six or eight hours and 20 to 30 mg. per kilogram of body weight of sodium sulfadiazine per twenty-four hours intramuscularly for seven to ten days. This procedure was carried out in all infants over 3 days of age and to all at any age

whose history or examination caused one to even suspect contact with infection or possible injury or abnormality. The results of this program were dramatic and appeared at once. With 631 admissions between 1948 and 1954, inclusive, the over-all mortality fell to 34 per cent and the percentage of those infants dying after one week of age fell from 32 to 7 per cent (see Table I).

TABLE I. AGE AT DEATH AND MORTALITY OF PREMATURE INFANTS IN THE CHILDREN'S HOSPITAL NURSERY BEFORE AND AFTER THE ACTIVATION OF A PROGRAM TO COMBAT INFECTION

AGE AT DEATH (DAYS)	1944-1947 (%)	1948-1954 (%)
0- 7	68	93
8-21	13	3
22-35	12	2
36+	7	2
Total admissions	508	631
Mortality	50%	34%

There is an increasing concern about deaths from infection occurring in the first hours or days after birth. These infections must be acquired in utero or during the birth process. In some cases it is suspected that premature rupture of membranes, vaginal examinations, stripping of the membranes, or operative manipulations may introduce the infection. In others, maternal disease may be the cause; however, in many, no likely etiological factor can be discovered.

Of the fifty-eight premature infant deaths that took place at the Boston Lying-in Hospital during the twelve months of 1952, only one death took place after the first week of life. Six of the premature deaths occurring in the first seven days of life were due to infection (10 per cent). Four of these infants had bronchopneumonia and died at the ages of 1¾, 4, 40, and 43 hours, respectively. One died at 40 hours with omphalitis. One died at five days with purulent *Esch. coli* meningitis and septicemia. Of the twenty-two full-term infant deaths, three were due to infection. Two of these infants died at 3 days of age, one with *Esch. coli* bronchopneumonia, and the other with *Esch. coli* septicemia. The third died at 48 hours with early bronchopneumonia. It is clear that the pediatrician must obtain a very careful history of possible infection in the mother during late pregnancy and labor and be prepared to institute prophylactic therapy in appropriate circumstances.

BLOOD DYSCRASIAS

Hemorrhagic disease of the newborn was once a popular and common diagnosis, but it is now of rare occurrence. It is now realized that this is not a true disease but a syndrome that can be due to many causes. As these causes, such as erythroblastosis, sepsis, anoxia, and trauma, are recognized, the bleeding is ascribed to its etiological cause and no longer referred to as hemorrhagic disease. A small residue of cases remain that appear to be caused by a true defect in the blood coagulation system such as congenital absence of fibrinogen. Such infants require careful study and supportive transfusions. The relation of vitamin K and abnormal prothrombin time to bleeding in the newborn infant is still not established. The rare bleeding referred to occurs with or without vitamin K having been administered to the mother and infant. There is need for a carefully controlled study to settle this relationship. Until such clarification is forthcoming, the point of wisdom would appear to be to con-

tinue administration of vitamin K to the mother before delivery and to the infant at birth.

Recent controlled studies[14] have proved the value of exchange transfusions in treating hemolytic disease of the newborn (erythroblastosis fetalis) as compared with single or multiple small transfusions. With exchange transfusions the mortality was 13 per cent, whereas in matched cases treated by single transfusion it was 37 per cent. These studies further demonstrated that the induction of labor three to five weeks before expected delivery in Rh-negative women resulted in a lower survival rate than when labor was allowed to proceed spontaneously.

Exchange transfusions have been shown to prevent the occurrence of kernicterus.[15] A microdetermination has been developed whereby bilirubin determinations can be performed on capillary blood. A correlation exists between the height of the bilirubin level and the occurrence of kernicterus. The bilirubin may act merely as an indicator of some other unknown substance responsible for the toxic damage to the brain. The bilirubin level rises very rapidly in the first few days of life in infants with hemolytic disease. Exchange transfusions, repeated if necessary, can lower the bilirubin level, and when this level has been kept below 20 mg. per 100 ml., kernicterus has not developed.

INCIDENCE OF PREMATURITY

The premature infant is defined as one weighing 2,500 grams (5 pounds 8 ounces) or less at birth. The number of premature infants in every 1,000 births to a large extent determines the over-all neonatal mortality rate. In this country there are countless maternity hospitals giving superb obstetric and pediatric care. Consider two such hospitals, delivering an equal number of infants, both hospitals having the same excellent neonatal rate for full-term infants of 4 per 1,000 live births, both hospitals having the same premature infant mortality rate of 15 per cent—yet one has a total neonatal mortality rate of 13 while the other has a high neonatal rate of 22 per 1,000 live births. The difference in rate is explained by the fact that the first hospital had a premature infant incidence rate of 6 per cent while the second had an incidence of 12 per cent. The first hospital therefore has 60 premature infants per 1,000 births with a 15 per cent mortality, thus 9 premature deaths to add to the 4 full-term deaths, giving a neonatal rate of 13 per 1,000 live births. The second hospital has 120 premature infants at 15 per cent mortality, or 18 premature deaths to add to the 4 full-term, or a neonatal rate of 22 per 1,000 live births. Some of us have the good fortune to work in hospitals with a low incidence of premature infants. We quote a low neonatal rate, yet in so far as caring for the actual baby in our nursery is concerned, we may be doing no better than our colleagues —we just do not have as many of the high-risk babies to account for.

The heart of the present premature problem is the number of small babies that are delivered in every 1,000 hospital births. The solution to the premature problem, obviously, would be to have every pregnancy continue to full term. Why are there premature infants and can anything

be done to reduce their incidence and why does the incidence vary from one hospital to another?

Studies on the incidence of prematurity have given valuable clues to the problem of the prevention of prematurity. Dunham[16] surveyed the scanty literature on this point up to 1948 and found the incidence of prematurity by birth weight to be between 7 and 11 per cent. From Potter's[3] data the incidence of prematurity was 6.4 per cent of 19,531 live-born infants at the Chicago Lying-in Hospital delivered from 1947 to 1952. The incidence of 2,500-gram-and-under infants among 24,327 live births from 1949 to 1953 at the Boston Lying-in Hospital was 7.3 per cent. The incidence of prematurity among 164,161 live births in New York City in 1952 was 8.8 per cent.[17]

Brown and associates[18] found the incidence of prematurity significantly increased by maternal illness, severe toxemia, eclampsia, mild bleeding, placenta previa, premature separation of the placenta, acute infections and chronic disorders of pregnancy. However, Bloch and co-workers,[4] in their recent survey of the problem, found that maternal illness had a negligible effect on the incidence of premature birth and concluded that its influence was most likely through its effect on maternal nutrition.

Ebbs and associates[19] found the incidence of miscarriages, premature births, and stillbirths to be greater in a group of women on poor diets. Burke and collaborators[20] evaluated the dietary history of 284 women, chiefly on the basis of protein intake, and found that all of the stillborn, all neonatal deaths but one, all of the premature infants but one, all of the functionally immature infants, and most of the congenital defects were found in the group of infants born to mothers with "poor" or "very poor" prenatal diets. Tompkins[21] gave 750 expectant mothers a special diet containing large amounts of proteins, vitamins, and minerals with definite limitation of fluids and water-embracing fruits. Not one case of prematurity occurred in this group, while there were thirty-seven cases in a similar group not on the special diet.

Bloch and associates[4] studying the incidence of premature births, live and stillborn, in ward and private patients, in Negro and white ward and private patients, and the influence of maternal and obstetric conditions associated with premature labor have confirmed the earlier findings of Eastman.[1] Both Eastman and Bloch emphasized the association between socioeconomic factors and the incidence of prematurity. In semiprivate patients the incidence of prematurity was 9 per cent, in the low economic group the incidence was 15.3 per cent. (At the Boston Lying-in Hospital, a private and semiprivate hospital, in 24,327 *live* births the incidence of prematurity was 7.3 per cent, while in a neighboring hospital admitting the low economic group the incidence was 12.3 per cent.) White private patients had an incidence of prematurity in total deliveries of 8.5 per cent; white ward patients 11 per cent; Negro private patients 10 per cent; and Negro ward patients 15 per cent.

Experience at the Boston Lying-in Hospital reflects the socioeconomic changes that have evolved in our population during the past thirty years. The present hospital began operation

in 1922 with 60 per cent of the 2,306 deliveries occurring in the patient's home (Fig. 1). Home deliveries were made without charge. The hospital of the admissions received free care. The number of home deliveries progressively decreased to the vanishing point in 1946. The private wing of

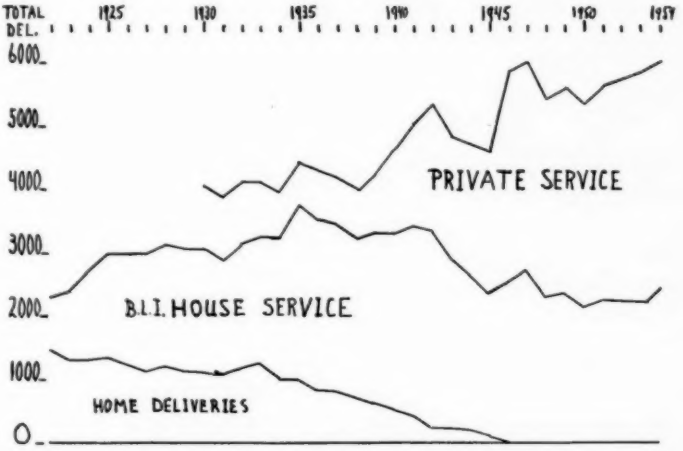

Fig. 1.—The changing proportion of home vs. ward vs. private deliveries at the Boston Lying-in Hospital between 1922 and 1954.

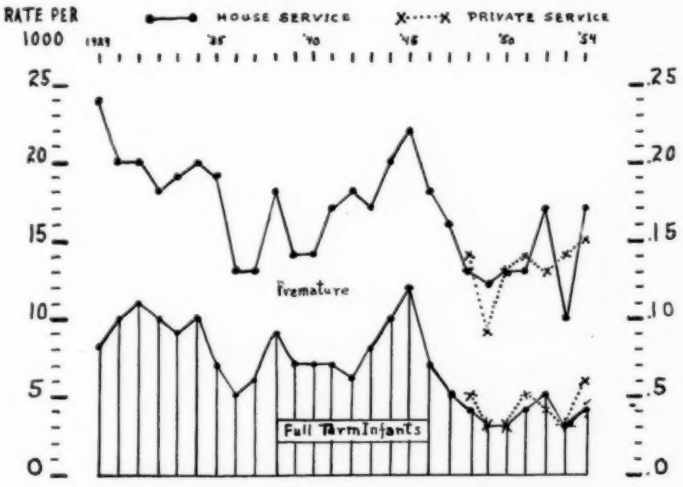

Fig. 2.—Neonatal deaths at the Boston Lying-in Hospital.

charges were from $21 to $35 per week, but deserving persons, unable to pay in whole or in part, were admitted and made payments according to their circumstances; 15 per cent

the hospital was opened in 1930. Of the 4,028 deliveries that year, 50 per cent were on the house service, 30 per cent were at home, and 20 per cent on the private wards. Although

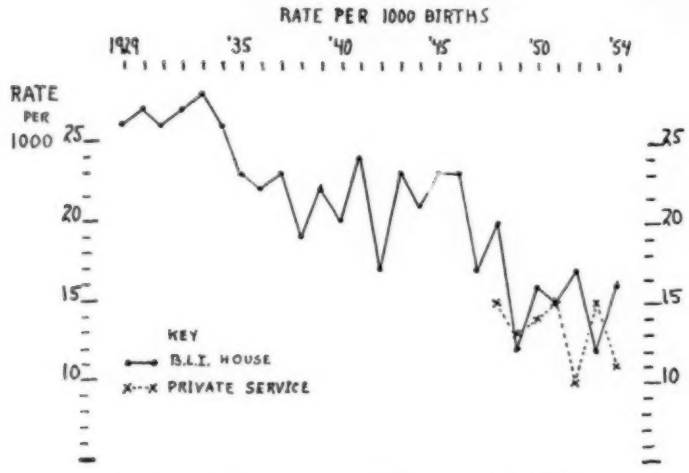

Fig. 3.—Viable stillbirth (28 weeks and over) mortality.

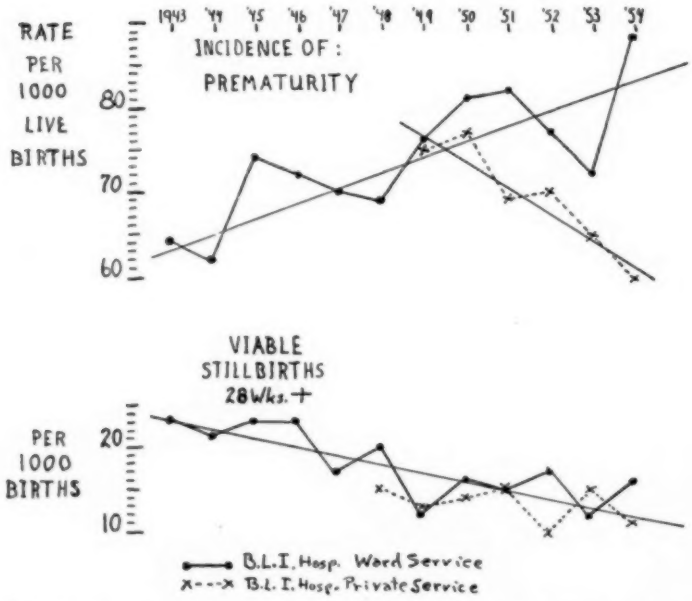

Fig. 4.—The incidence of liveborn premature infants and viable stillbirths at the Boston Lying-in Hospital from 1943 through 1954.

home deliveries disappeared, the number of patients delivered per year on the house service has remained almost constant, averaging 2,400. The striking change has been the steady increase in private patients, from 944 in 1930 to 3,577 in 1953. It is our impression that with improved economic circumstances everyone wants to have their own private obstetrician and to be on the private service; failing in this, they seek hospital delivery on the house staff service.

There has, during this period, been a 50 per cent reduction in the total neonatal mortality, the full-term and the premature infant neonatal mortality rates (Fig. 2). There has also been a 50 per cent reduction in the "viable" stillbirth rate (fetuses of 28 completed weeks' gestation and over) (Fig. 3).

It may be more than chance that the sharp reduction in deaths in both liveborn and stillborn infants began in 1946 and coincides with disappearance of home delivery and the sudden increase in the number of private patients—a testimonial to the improved socioeconomic conditions in our local population.

We have been witnessing an interesting and baffling phenomenon—the incidence of prcmaturity on our ward service has increased from 6.3 to 8.3 per cent in the last ten years, a rate that cannot be explained by the reduction in stillbirths (Fig. 4). At the same time the stillbirth rate and incidence of premature infants in our private patients are both falling simultaneously. Perhaps it is a reflection of greater improvement in conditions affecting the private group that has not yet had time to influence the new members of the ward group on their climb up the socioeconomic ladder. Even though the incidence of prematurity is increasing in the one group and decreasing in the other, the actual mortality of the liveborn premature infant in both groups is equal and unchanged from the rate experienced over the past ten years (13 to 15 per cent).

SUMMARY AND CONCLUSIONS

While the neonatal mortality rate for the United States has been reduced 40 per cent from 1935 to 1951, the present rate of 20 per 1,000 live births still has a long way to go to equal the 13 per 1,000 observed in many specialized maternity hospitals. A summary of present obstetric and pediatric knowledge by which this further reduction may be accomplished is presented.

The importance of socioeconomic factors in past, present, and future efforts to solve the premature problem is discussed. Bloch's[4] statement is a pertinent conclusion to this presentation: "The occurrence of premature birth is primarily a public health problem concerned basically with the socioeconomic status and nutritional condition of the pregnant mother."

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EPIDEMIC NEPHRITIS AT RED LAKE, MINNESOTA

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ACUTE glomerulonephritis, like rheumatic fever, is considered a nonsuppurative complication of infection by the beta hemolytic streptococcus, group A. Rheumatic fever, however, occurs in a relatively constant incidence of about 3 per cent, regardless of serologic type or clinical manifestations of the antecedent infection, and in this country is commoner in the northern and southern states, in the colder months, and in families with a history of susceptibility to the disease. Nephritis, on the other hand, is characterized by an extremely variable attack rate which apparently is not influenced by host susceptibility or geographic and climatic factors. Although usually sporadic, nephritis may appear from time to time in widespread epidemics or localized outbreaks in small segments of the population, and in families apparently without hereditary predisposition.

The reports of numerous investigators,[1-13] notably those of Rammelkamp's group, suggest that differences in epidemiologic features between rheumatic fever and nephritis may be explained by variations in bacterial factors. It is thought that although most, perhaps all, types of group A streptococci can produce rheumatic fever, only a few may be nephritogenic.[1-4] Infection by type 12 is attended by a particularly high attack rate of nephritis; other types, as 2, 4, 17, 18, 22, 31, and perhaps 25, also have been implicated. Different serologic strains, however, are known to vary in biologic properties. Rammelkamp and Weaver[1] have called attention to evidence[13-15] suggesting that even the various strains of type 12 may differ in nephritogenic capacity. The type 12 organisms isolated by Saslaw and Streitfield[16] in Miami school children, for example, appeared to be neither rheumatogenic nor toxic to the kidneys.

Acute nephritis is generally of sudden onset, the symptoms appearing about ten or twelve days after an operation or subsidence of scarlet fever or streptococcal infection of the throat, tonsils, sinuses, middle ear or skin (as pyoderma, impetigo). Rammelkamp[3] suggests that some indefinite biologic characteristic of certain strains of types 12 and 4 may render the organisms unusually invasive to the skin and other tissues.

In the classical case of glomerulonephritis, cardiorenal damage is indicated by albuminuria, hematuria, edema, and hypertension. In some patients hematuria is the only manifestation. The renal lesions may soon heal, with recovery; or the attack may subside and remain latent without complete healing for varying periods, after which recovery may ultimately take place. If the inflamed tissues do not

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heal, the disease may again become active, with increasing involvement of the nephrons and progression to the degenerative and later the terminal stage, with death in uremia. In some cases the patient may pass directly into the terminal from the latent stage.

Two epidemics of acute glomerulonephritis were investigated by the Epidemic Intelligence Service of the Communicable Disease Center, U. S. Public Health Service, in the year 1953.

RED LAKE EPIDEMIC

This report is concerned with the epidemiology of an outbreak on the Red Lake Indian Reservation in northern Minnesota during the summer and fall of 1953. The clinical aspects of this epidemic, which totaled sixty-three cases, have been described.[17]

The reservation, comprising 900 square miles of isolated "Indian country" (Fig. 1), is the home of the Red Lake band of the Chippewa tribe, approximately 2,800 in number. The population is mainly concentrated in three villages—Red Lake, Redby, and Ponemah—located on the shores of Red Lake.

The social and political importance of this Indian community lies in the fact that it is one of the last of the "closed" reservations. The governing body of the band is the tribal council of chiefs; the reservation is operated under Indian law with Indian police and courts. Thus the Chippewa mores, their tribal customs and folkways, their spoken language and primitive religion (sun worship) are perpetuated. Medicine men of the band still practice their ancient rites.

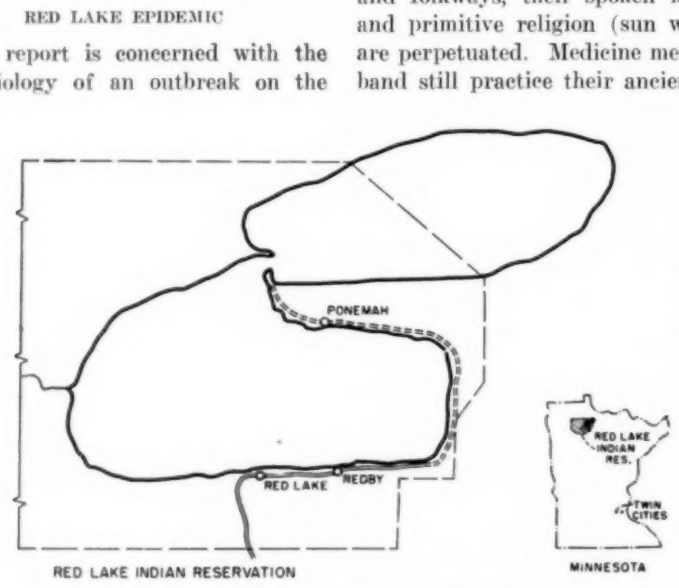

Fig. 1.—Red Lake Indian Reservation.

A senior medical officer* of the Indian Service, however, is responsible for the health of the reservation, and medical care for the inhabitants is provided at the Red Lake Indian Hospital—a frame building with twenty beds. Despite inadequacy of facilities, an excellent standard of medical care is maintained.

*Dr. Herman Kleinman, Senior Physician, Red Lake Indian Hospital.

In June, two children on the reservation became ill with scarlet fever, the first in five years. In July, five additional cases were reported to the Branch of Health, Bureau of Indian Affairs. Two patients, although having none of the usual pharyngeal symptoms, showed marked pyodermatous lesions, which had been present about a week before appearance of the characteristic rash. Concurrently, with the development of these cases, acute glomerulonephritis began to appear.

At the same time it became evident that pyoderma was widespread among the preschool children and those of school age. Pyoderma in itself is not unusual in Indian children during the summer, but the eruption seen in this epidemic was of unique and uniformly characteristic appearance and distribution. The lesions, round, raised, pale red in color and 5 to 7 mm. in diameter, were distributed over the lower trunk and lower extremities. In the center of each a pinhead-sized vesicle containing clear serous fluid developed, which ruptured, forming a thin flat crust over the vesicular area. The lesions did not become confluent or grossly purulent, but assumed irregular outlines and became heavily crusted when secondary infection occurred. On standard treatment with penicillin healing was rapid but recurrence was common. Depigmentation was frequently noticed after healing.

Little attention was paid to the pyoderma at first because of other medical problems of seemingly greater importance. Dysentery caused by *Shigella sonnei* had been epidemic for several months, and, in addition to the scarlet fever and acute glomerulonephritis in the population, several cases of infectious hepatitis had developed.

In July, after nephritis had been diagnosed in eight cases, the senior medical officer issued a formal request for aid in determination of the etiological chain and institution of control measures, but help was delayed. The request for assistance did not reach the Communicable Disease Center until the second week in September, when it was immediately translated into action. Dr. Elaine Updyke and I arrived at Red Lake Hospital on September 10. By that time the tally of nephritis cases, which at the end of August had been twenty-four, had now risen to thirty-eight. Scarlet fever had developed in twenty-two patients.

Laboratory facilities essential to proper epidemiologic investigation of the outbreak were not available locally. Those at hand were inadequate for even the minimum of bacteriologic studies required. Therefore, a field laboratory was set up by Dr. Updyke in Minneapolis, 280 miles away. Studies were begun immediately, and arrangements were made to transport supplies and relay cultures to the field laboratory by local air line, which operates one flight a day between Minneapolis and Bemidji, the town nearest the reservation.

All positive cultures obtained in this study were sent to the Streptococcus Laboratories of the Communicable Disease Center, U. S. Public Health Service, Chamblee, Georgia, for further grouping and typing. The findings will be reported in detail by Dr. Updyke in a separate communication.

METHOD

The investigation was limited to fifty-six of the sixty-three cases of

nephritis previously reported.[17] Of the seven cases not included in this study, six were subsiding at the time of diagnosis and one was complicated by hepatitis.

Fifty-four (96 per cent) of the patients were 1 to 8 years of age, the average age being about 4 years. There was about the same number of males as females.

The cases were almost evenly distributed among the three villages on the reservation. In conformance to the findings of others in previous studies, no particular geographic factors seemed to be involved in the spread of this epidemic.

Pyodermatous lesions, as described, were present in 80 per cent. There was little correlation between age or sex and the occurrence of pyoderma.

In a *preliminary survey*, the home of each patient with glomerulonephritis was visited, and pertinent information recorded on previous illness, symptoms, and contacts. Nose and throat cultures were obtained from 350 individuals, nine of whom were cultured more than once (Table I). This total includes two groups:

(1) Two hundred sixteen persons at Red Lake, of whom (a) 51 were known to have nephritis; (b) 141 were contacts (nephritis developed later in 3 of these); and (c) 24 were suspected cases (patients with albuminuria, also pharyngitis and tonsillitis).

TABLE I. PRELIMINARY SURVEY OF NOSE AND THROAT CULTURES FROM 350 INDIVIDUALS

	PRELIMINARY POSITIVE (NOT CONFIRMED)	NEGATIVE	POSITIVE		PER CENT CONFIRMED
Cases (51)	4	33	14	A— 8 G— 4 C— 2	29.8
Contacts (141)	1	117	23	A—11 G— 5 C— 7	16.4
Suspects (24) (albuminuria, also pharyngitis and tonsillitis)	1	13	10	A— 8 C— 2	43.5
Total (216)	6	163	47	A—27 G— 9 C—11	22.4
Comparison of cultures from children of first grade					
Red Lake	1	47	15	A— 3 G— 4 C— 8	24.2
Cass Lake		62	9	A— 6 G— 2 F— 1	12.7
Total (134)	1	109	24		

There is no statistically significant difference in these rates when tested by a χ^2 test.

(2) One hundred thirty-four controls, first-grade school children, of whom (a) 63 were Indians from the Red Lake Reservation, and (b) 71 were Indian and non-Indian from Cass Lake, over 50 miles away. None in this group had had scarlet fever, nephritis, or pyoderma.

Cultures were also taken from the pyodermatous lesions of twenty-six individuals on the Red Lake Reservation, twelve of whom had nephritis. (Three

of these patients had been treated before culture.) (Table II.)

Results of the Preliminary Survey.—Of nose and throat cultures taken in fifty-one active cases of glomerulonephritis, 29.8 per cent were positive for the beta hemolytic streptococcus (group A in eight cases). Before culture, most of these patients had been treated in the conventional way with 300,000 units of a respository type penicillin every other day.[17] For the 141 contacts, 16.4 per cent of the cultures were positive (group A in eleven cases), and for the twenty-four suspects, 43.5 per cent of the cultures were positive (group A in eight cases). Of the cultures for the total group of 216 individuals, 22.4 per cent were positive for the beta hemolytic streptococcus (group A in 27 cases) (Table I).

In the survey of the 134 first-grade controls, 24.2 per cent of nose and throat cultures in sixty-three subjects at Red Lake were positive for the beta hemolytic streptococcus (three group A); and of the seventy-two subjects cultured at Cass Lake, 12.7 per cent were positive (six group A).

Cultures of pyodermatous lesions taken from twenty-six individuals at Red Lake were positive for group A in fourteen cases (53.8 per cent) (Table II). Of the twelve patients with nephritis as well as pyoderma in this group, seven yielded positive cultures for group A. All group A organisms isolated from these patients were untypable against known antisera.

TABLE II. PRELIMINARY SURVEY OF CULTURES OF SKIN LESIONS FROM TWENTY-SIX INDIVIDUALS*

Number positive	14 (53.8%)	All group A, untypable
Number negative	12	This includes 1 positive for group C
Total cultured	26†	

*Two of these patients were cultured twice, so that actually there were 28 cultures (15 positive, 13 negative).

†Twelve of the 26 cultured had nephritis. Of these 12, 3 had been treated. There were 7 positive (A, untypable) cultures from the 12, and 5 negative.

MASS PROPHYLAXIS

Earlier reports[18, 19] have suggested that adequate penicillin treatment of streptococcal infection may forestall or at least modify and attenuate subsequent glomerulonephritis. Rammelkamp[3] also has repeatedly claimed that the attack rate of nephritis, as well as of rheumatic fever, will be reduced by administration of penicillin for infections by group A streptococci. In view of our results in the preliminary survey at Red Lake, it was concluded that mass prophylaxis against beta hemolytic streptococcal infection was desirable, especially for the younger, and therefore most vulnerable, inhabitants of the reservation. The importance of maintaining a continuous penicillin effect for a length of time sufficient for suppression of the organism has been stressed.[18] Chamovitz and associates,[22] co-workers of Rammelkamp, in evaluating the antistreptococcal action of a single injection of benzathine penicillin for prevention of rheumatic fever, have reported that one dose of this compound, an insoluble salt of penicillin with antibiotic effect persisting up to thirty days,[20, 21, 22] eliminated the organism more completely than did three doses

of a repository type preparation of procaine penicillin with aluminum monostearate, one given every other day. Therefore, benzathine penicillin* was obtained for the prophylactic program at Red Lake through the cooperation of a large pharmaceutical house.

To evaluate the effectiveness of prophylaxis it was decided to culture the noses and throats of approximately one-fourth of the individuals to be treated in the program before administration of the drug, and again to culture the same subjects after several weeks.

Early in October my associates and I returned to Red Lake to take the necessary cultures and administer the penicillin. We were assisted by nurses from local organizations and the state department of health.

The prophylactic series included 1,997 individuals—over 70 per cent of the Red Lake population. Approximately 500 of this group were cultured before injection. A representative (systematic) sample was obtained by culturing every fourth person to be treated, regardless of age or sex. Benzathine penicillin was then given to each in a single dose, by injection—600,000 units to children less than 15 years old, and 1,200,000 units to subjects 15 years of age or older.

Approximately one month later the same team of workers returned again to the reservation and recultured as

TABLE III. BETA HEMOLYTIC STREPTOCOCCUS INFECTION. NOSE AND THROAT CULTURES BEFORE PROPHYLAXIS

AGE GROUP (YR.)	NUMBER OF CULTURES	NUMBER POSITIVE	PER CENT POSITIVE EACH AGE GROUP
0-4	83	10	12.05
5-9	86	29	33.72
10-14	66	27	40.91
Total through 14 years of age		66 positive cultures (83.5% of total positive)	
15-19	29	6	20.69
20 plus	117	7	5.98
Total	381	79	*Entire Group* 20.73
Nose and Throat Cultures One Month After Prophylaxis			
Total	381	5	1.3

All patients with positive cultures at the first sampling were negative at the second.

TABLE IV. GROUP A, UNTYPABLE, CULTURES BEFORE PROPHYLAXIS

AGE GROUP (YR.)	NUMBER CULTURES	NUMBER POSITIVE	PER CENT POSITIVE EACH AGE GROUP
0-4	83	7	8.43
5-9	86	11	12.79
10-14	66	15	22.73
Total through 14 years of age		33 positive cultures (80.5% of total positive)	
15-19	29	2	6.90
20 plus	117	6	5.13
Total	381	41	*Entire Group* 10.8
Cultures One Month After Prophylaxis			
Total	381	1	0.3

*Bicillin, long-acting injection, benzathine penicillin G (dibenzylethylenediamine dipenicillin G) in aqueous suspension, was supplied by Wyeth Laboratories.

many as possible of the individuals previously cultured. A total of 381 paired cultures were thus obtained.

Results of Mass Prophylaxis.—Of 381 cultures taken just before injection, seventy-nine (20.7 per cent) were positive for the beta hemolytic streptococcus (Table III). One month after prophylaxis only five (1.3 per cent) were positive. All of the patients showing positive cultures at the first sampling were negative at the second.

In further grouping and typing of the seventy-nine positive cultures at the Streptococcus Laboratory of the Communicable Disease Center, forty-one (10.8 per cent) were found to be group A, untypable against any of the known antisera. At the second survey, one month after prophylaxis, however, only one culture (0.3 per cent) fell into this category (Table IV).

The majority of cultures positive for the beta hemolytic streptococcus were obtained in subjects up to 14 years old (83.5 per cent) (Table III). The same is true for the cultures positive for group A, untypable. In this case thirty-three cultures (80.5 per cent) positive for untypable group A organisms were obtained in subjects up to 14 years old (Table IV).

Of the 381 subjects from whom paired cultures were obtained, one before and one about a month after prophylaxis, sixty-five (17.1 per cent) had active or healing pyoderma at the time of the first culture. This will be recognized as a very large percentage when it is realized that the patients who had had pyoderma and whose lesions were already healed were not included, even though their skin manifestations may have been noted.

The data on cultures from the skin lesions of patients with pyoderma are given in Table V. Although the age distribution is slightly different from that demonstrated for the presence of beta hemolytic streptococci in the nose and throat (Tables III and IV), there is a basic similarity between these tables; that is, the majority (85 per cent) of positive cultures were obtained from children 14 years old or younger.

TABLE V. PYODERMA PRESENT AT TIME OF PROPHYLAXIS. PATIENTS CULTURED IN BOTH SURVEYS

AGE GROUP (YR.)	NUMBER CULTURED (BOTH SURVEYS)	NUMBER POSITIVE	PER CENT POSITIVE ACTIVE OR HEALING
0-4	83	20	24.1
5-9	86	20	23.3
10-14	66	15	22.7
Total through 14 years of age			55-85%
15-19	29	1	3.4
20 plus	117	9	7.7
Total	381	65	17.1

Four cases of pyoderma were noticed at the time of the postprophylaxis survey, but not one was characterized by lesions typical of the pyoderma associated with nephritis. These few cases probably were the result of insect bites or other superficial infections.

The epidemic of glomerulonephritis was aborted within two weeks of the prophylactic program. The last diag-

nosed case was seen in a subsiding phase a day or two after the postprophylaxis survey was completed.

Apparently the medication had some effect also on the control of other diseases as well. No scarlet fever or pyoderma of the type described have been reported since administration of mass prophylaxis.

The epidemic curve is shown in Fig. 2, together with the distribution of scarlet fever cases over the same period.

Ninety-six per cent of the nephritic patients were 1 to 8 years old, with an average of 4 years.

In a preliminary survey to determine the etiological agent in the epidemic, nose and throat cultures were taken from 350 individuals: 216 at Red Lake (fifty-one nephritic patients, together with contacts and suspects; and a control series of 134 first-grade school children [sixty-three from Red Lake and seventy-one from Cass Lake]). Pyodermatous lesions

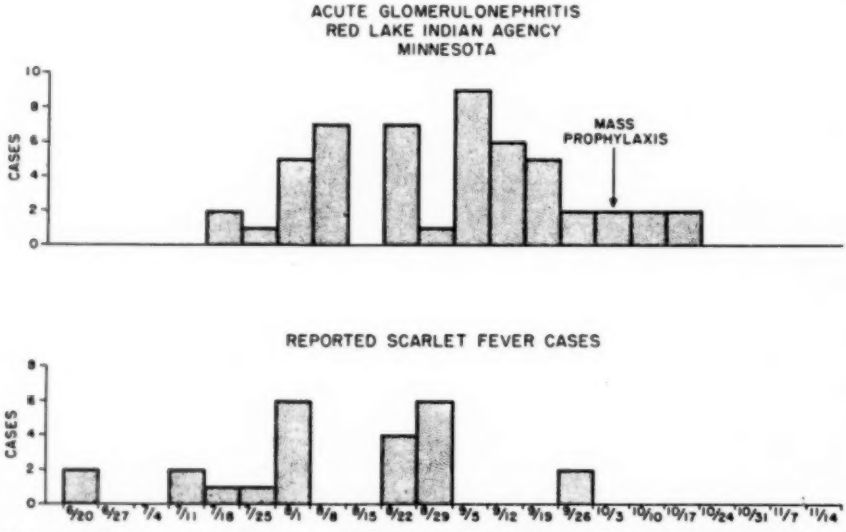
ACUTE GLOMERULONEPHRITIS
RED LAKE INDIAN AGENCY
MINNESOTA
CASES
MASS PROPHYLAXIS
REPORTED SCARLET FEVER CASES
CASES
6/20 6/27 7/4 7/11 7/18 7/25 8/1 8/8 8/15 8/22 8/29 9/5 9/12 9/19 9/26 10/3 10/10 10/17 10/24 10/31 11/7 11/14

Fig. 2.—Epidemic curves for acute glomerulonephritis and scarlet fever. Cases by date of onset.

SUMMARY

The epidemiology of fifty-six cases of classical acute glomerulonephritis, occurring at the Red Lake Indian Reservation in northern Minnesota in the summer and fall of 1953, was studied by the Epidemic Intelligence Service of the Communicable Disease Center. In 80 per cent of the patients a unique type of pyoderma was also present. Scarlet fever preceded some cases. of twenty-six individuals, including twelve with nephritis also were cultured.

Of the 216 subjects cultured at Red Lake, 22.4 per cent were positive for the beta hemolytic streptococcus. Of the sixty-three first-grade school children at Red Lake, 24.2 per cent harbored the beta hemolytic streptococcus, whereas the organism was present in cultures of only 12.7 per cent of those

from Cass Lake. Cultures of the pyodermatous lesions were positive for beta hemolytic streptococci, group A, in 53.8 per cent. All group A organisms were untypable against known antisera.

Mass prophylaxis of over 70 per cent of the Red Lake population was instituted to control the epidemic. Benzathine penicillin was administered by injection, in a single dose of 600,000 units to each subject less than 15, and 1,200,000 units to those of 15 years or older. Previous to injection, nose and throat cultures were taken from about 500 of the individuals who were to receive prophylaxis. About one month later as many as possible of these subjects were recultured. Three hundred eighty-one paired cultures were thus obtained.

Cultures were positive for the beta hemolytic streptococcus in 20.7 per cent before prophylaxis, and on reculture, only 1.3 per cent were positive. All positive cultures at the first sampling were negative at the second. Of cultures before prophylaxis, 10.8 per cent were group A, untypable; after prophylaxis, untypable strains of group A were present in only 0.3 per cent.

Of cultures positive before prophylaxis, 83.5 per cent were obtained from subjects up to 14 years old. Of cultures positive for untypable group A organisms before prophylaxis, 80.5 per cent were obtained in the same age group. Eighty-five per cent of positive cultures from the pyodermatous lesions were also obtained from children up to 14 years of age.

CONCLUSIONS

Mass prophylaxis with benzathine penicillin aborted, within two weeks, an epidemic of nephritis apparently caused by a previously unidentified strain of the beta hemolytic streptococcus, group A, with strongly nephritogenic properties. Acute glomerulonephritis, therefore, is a preventable disease.

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An Early Treatment for Rickets

In the Rickets the best Corrective I have ever found is a Syrup made of Black Cherrys. Thus. Take of Cherrys (dry'd ones are as good as any) & put them into a vessel with water. Set the vessel near the fire and let the water be Scalding hot. Then take the Cherrys into a thin Cloth and squeeze them into the Vessel, & sweeten the Liquor with Melosses. Give 2 Spoonfuls of this 2 or 3 times in a day. If you Dip your Child, Do it in this manner: viz: naked, in the morning, head foremost in Cold Water, don't dress it Immediately, but let it be made warm in the Cradle & sweat at least half an Hour moderately. Do this 3 mornings going & if one or both feet are Cold while other Parts sweat (which is sometimes the Case) Let a little blood be taken out of the feet the 2nd Morning and that will cause them to sweat afterwards. Before the dips of the Child give it some Snakeroot and Saffern Steep'd in Rum & Water, give this Immediately before Diping and after you have dip't the Child 3 Mornings Give it several times a Day the following Syrup made of Comfry, Hartshorn, Red Roses, Hog-brake roots, knot-grass, pennyroyal roots, sweeten the Syrup with Melosses. Physicians are generally fearful about diping when the Fever is hard, but oftentimes all attemps to lower it without diping are vain. Experience has taught me that these fears are groundless, that many have about diping in Rickety Fevers; I have found in a multitude of Instances of diping is most effectual means to break a Rickety Fever. These Directions are agreable to what I have practiced for many years.

LETTER TO THE REV. JOSEPH PERRY OF WINDSOR, CONNECTICUT, 1769.

ELECTROENCEPHALOGRAPHIC STUDIES FOLLOWING PERTUSSIS IMMUNIZATIONS

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MADSEN[1] of Denmark was the first worker to report catastrophic neurological reactions due to whooping cough vaccinations. Similar reactions have been described from several other European countries, Britain, France, and Switzerland, and the United States. The main neurological symptoms are changes in consciousness varying from marked drowsiness to deep coma and convulsions. Considering the large number of babies that receive active immunizations for pertussis every year, the number of affected children is small but the outlook for these children is so bad that this problem needs more study as to frequency, severity, and preventability. Toomey[2] sent questionnaires to a number of interested clinicians in an attempt to find out how often convulsions occurred following pertussis vaccinations. He received reports on thirty-eight cases; some of those cases were not pertinent to the study because other possible causes for convulsions were present at the time, e.g., high fever due to an infection or an active case of whooping cough at the time of the injection. Of his thirty-eight positive reports, the most important ones were the cases of Dr. Douglas Buchanan of Chicago who reported "twelve cases in the last few years; some decerebrate rigidity; death" and one case each contributed by Bien and Stetin characterized by convulsions and death. Byers and Moll[3] of Boston published a detailed report on fifteen children who showed neurological deficits in the acute phase after whooping cough vaccinations over a ten-year period. They had been followed for from a few months to several years; estimation of their mentality was made, important physical findings were noted, and also air studies in most of these children were done. Out of thirteen survivors, eleven had seizures at the time of the follow-up, a twelfth had had seizures up to five months after the last injection and apparently was still on anticonvulsant therapy at the time of publication, and the thirteenth (Case 6) stopped having seizures after his hospitalization but was reported to be spastic and imbecile. Livingston[7] mentions in his new book on convulsive disorders in children having seen seven children with recurrent seizures following pertussis immunizations. He does not give more details except that those cases were similar to those of Byers'. Köng[4] collected eighty-two cases from the literature and added two of his own; he tabulated the ages and order numbers of injections and the amount and type of vaccine, whenever this information was available. Toomey's thirty-eight cases are included in

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Köng's series, and on reviewing the latter's and Toomey's references, it is evident that six or seven cases should be subtracted from the eighty-two because they are also listed by Toomey.

On analyzing Köng's series, including Byers' and Moll's, and adding Sutherland's[5] case and my own (see below), one gets the following information:

Ages.—

Newborn period	2
1 through 6 mo.	10
7 through 12 mo.	17
Over 12 mo.	4
Over 2 yr.	1

This experience does not mean that children under 1 year are more likely to be damaged; it is simply the age at which most children are immunized.

Number of Injections.—

First	16
Second	18
Third	16
Fourth	1

When one child reacted to more than one shot, I tabulated the first injection to which he responded unfavorably. Brody's[6] first case showed neurological changes following each of four shots.

Time of First Symptoms.—

Within 6 hr.	15
7 to 12 hr.	12
13 to 18 hr.	3
19 to 24 hr.	4
Over 24 hr.	4

Because many of the children were seen by the reporting physicians after the acute stage, it is possible that some changes of consciousness or marked irritability may have started earlier than related. The important point here is that the symptoms are likely to become manifest in less than twenty-four hours, and sometimes immediately. This is in marked contrast to the delayed reaction that occurs with encephalitis due to smallpox vaccination.

Kind of Vaccine.—Fluid, alum precipitated, pertussis with diphtheria, and pertussis with diphtheria and tetanus are used. The reported dosages vary from 2 to 40 billion organisms per injection.

CASE REPORT

L. P. (No. 52-1663, St. Mary's Hospital, Racine, Wis.) was born following a normal pregnancy, had been examined monthly following birth and was found normal in every respect. This girl was given ½ c.c. of Squibb's alum-precipitated DPT into the right deltoid area in February, 1952. Approximately twelve hours after that injection she had a brief convulsion. When she returned for her second injection, four weeks later, on March 18, 1952, she was found to be normal and responded the way 6-month-old babies are expected to do. The mother did not report the convulsive episode at that time, and the injection was repeated following the physical examination, this time into the left deltoid muscle. Twelve hours later she started having severe convulsions for which she was transferred to the hospital. She went into a state of decerebrate rigidity and continued having many convulsive seizure in spite of treatment with intramuscular phenobarbital, ether, Sodium Pentothal, oxygen, repeated tracheal toilet and intravenous glucose. She died twelve hours after the onset of the first symptoms. Her spinal fluid was clear, contained no leukocytes, and globulin was not increased. At necropsy (performed by Dr. Myron Schuster) all organs were normal except the brain. It weighed 820 grams and appeared normal externally; the meningeal vessels were congested. Microscopic examination of the cerebral hemispheres showed the meninges to be hyperemic and also a

slight increase in cellularity, the cells being mononuclear (lymphocytes). There was a prominent subcortical cellular vacuolization which suggested that these elements were swollen and had subsequently shrunk by fixation.

"The vascular components of this tissue are uniformly very congested. Although the perivascular lymph spaces are dilated, there is no cellular exudation into these spaces. However, in two of these sections the vessels in the white matter are so engorged that there has been extravasation of red cells into surrounding tissue, forming microscopic petechial hemorrhages. In the section of basal ganglia which included the wall of the third ventricle, there is a subpendymal increase in cellularity which appears to be oligodendroglia proliferation.

"The ganglion cells do not appear to be distorted. Section of the medulla shows nonspecific features of marked diffuse vascular engorgement without cellular inflammatory exudate.

"Section of the cerebellum shows normal folia, orderly arrangement and good preservation of the various cell layers. The white matter of the cerebellum shows vacuolization suggestive of edema; the vessels are uniformly engorged. No exudative process is found."

The present study was undertaken in an attempt to find out whether evidence of changed cerebral physiology due to pertussis vaccinations could be found more often than clinically recognizable symptoms. Grossman and associates[8] have shown that electroencephalographic changes may occur in some cases of measles even when a changed sensorium, stiff neck, convulsions or other clinical evidence of encephalitis was absent.

MATERIAL AND METHOD

Electroencephalograms were recorded before and after pertussis immunizations in eighty-three cases.

In all but three cases the tracings were obtained with the child awake and also during sleep. Electrodes were applied to the frontal, parietal, temporal, and occipital areas on each side and to both ears. The interconnected ears were used as a common reference electrode (monopolar recording). All tracings were made with a Grass 8-channel console. Normal and abnormal electroencephalograms were judged according to the standards for age as given in Gibbs' *Atlas*.[9]

Each child served as his own control; if any changes occurred, they would appear from a comparison of the before and after recordings. None of the subjects used in this study had had any kind of immunization before the first electroencephalogram. The rectal temperature was taken before the second electroencephalogram was recorded.

Forty children had been referred from the Chicago Board of Health through the courtesy of Dr. Herman Bundesen. They received in the deltoid or gluteal area ½ c.c. of the vaccine containing 15 billion organisms, including diphtheria and tetanus toxoid, alum precipitated. The remaining forty-three patients who had been sent from the Central Free Dispensary of the Presbyterian Hospital of Chicago (Chief of Service: Dr. H. Sanford) were given 1 c.c. of alum-precipitated pertussis vaccine containing 30 billion organisms without diphtheria and tetanus.

TABLE I. AGE DISTRIBUTION OF GROUP UNDER INVESTIGATION

Under 3		2
3 through 6 mo.		74
7 through 9 mo.		3
9 through 12 mo.		3
Over 12 mo.		1
Youngest	2 mo.	25 da.
Oldest case	15 mo.	28 da.

TABLE II. TIME INTERVAL BETWEEN THE INJECTIONS AND THE BEGINNING OF THE SECOND ELECTROENCEPHALOGRAM*

16½ through 19 hr.	59
19 through 24 hr.	18
24 through 48 hr.	5
48 through 72	1
Longest 72 hr.	

*No child was re-examined after less than 16½ hours, only one after more than 48 hours.

TABLE III. RECTAL TEMPERATURE IMMEDIATELY BEFORE THE SECOND ELECTROENCEPHALOGRAM

Over 100° F.	13
Over 101° F.	4
Over 102° F.	1
Over 103° F.	1
Highest recorded temperature 103.8° F.	

TABLE IV. ASSOCIATED DATA LIKE CONGENITAL DEFECTS, SIBSHIP, PREMATURITY

Twins: 1 set	Nystagmus: 1
Siblings other than twins: 1 set	Cleft palate: 1
Mongoloid: 1	Difficult resuscitation: 1
Premature: 4	

RESULTS

All children except Cases 51, 75, and 79 were found to be normal before and after the immunizations; the electroencephalograms taken on the following day were not different from those taken before.

Case 51 was a 5-month-old girl whose paternal uncle used to have convulsions with fever as a young child and whose 2-year-old brother is subject to frequent convulsions without fever. Her preinjection electroencephalogram which showed a basic frequency of 4 to 6 per second is perfectly normal at this age. She received her immunization at 4:25 P.M. on Sept. 16, 1954. At 9:25 A.M. the next day her rectal temperature was 99° F. and her tracing was much slower than the day before. The decreased frequency was apparent in recordings awake and asleep but was most evident when she was awake. A second repeat electroencephalogram on September 18 showed even more slowing than on September 17. The slowing was diffuse in all leads without any reliable focus. One week later (on September 25) all frequencies were almost identical with those of the preinjection recording and the electroencephalogram was classified as normal. The child had been alert and happy during that period of observation and the parents had not noticed any untoward symptoms, especially increased fretfulness, drowsiness, fever, or convulsions. This patient belonged to the series from the Presbyterian Hospital and had received pertussis vaccine alone.

Case 79 showed a perfectly normal electroencephalogram before receiving a DPT immunization. At the time of the repeat electroencephalogram the following day when she had a rectal temperature of 103.8° F., there was a moderate slowing in all leads awake and much abnormally slow activity during drowsiness and sleep. She showed no other clinically recognizable reaction, and was found well and afebrile another twenty-four hours later.

Case 75 showed no changes after the injection but is mentioned because it was the only case that showed abnormality before the injection. The abnormality consisted of a slow wave focus in the right occipital area; it was present and identical in both examination.

DISCUSSION

Death or very severe permanent brain injury are examples of the most extreme reactions to pertussis vaccine. In addition to these cases it

seems likely that milder but possibly significant brain reactions may develop. The present series is not large enough to give per centum figures on electroencephalographic changes in cases receiving pertussis vaccine, but it shows that definite changes can occur in the absence of clinical symptoms. These electroencephalographic changes are not severe or frequent enough to abandon routine whooping cough immunizations, but they emphasize the need for an improved, nontoxic pertussis vaccine.

While Byers reported fifteen cases of brain damage due to pertussis immunizations in ten years, he also reports twenty-six cases of encephalitis due to whooping cough itself in the same period. Toomey,[2] Byers,[3] and Cockburn[12] from the Central Public Health Laboratories of London, England, recommend that pertussis immunizations should not be used in children with convulsions or other abnormal neurological findings. But Melin[10] reported ten children whose seizures were much worse after an attack of whooping cough. He strongly recommends that even children with seizures should be immunized against whooping cough because the risk of pertussis is even greater than the risk of immunization. Sauer[11] suggested that if immunizations were desirable in spite of a history of previous convulsions, fractional doses should be tried at monthly intervals.

SUMMARY AND CONCLUSIONS

The literature on severe neurological reactions to pertussis vaccine was reviewed and summarized, and another case of fatal outcome was reported.

In the present study, eighty-three children between the ages of 2¾ and 16 months had electroencephalograms done before and after their first whooping cough immunization.

Forty-three children had been injected with plain pertussis vaccine containing 30 billion organisms and the remainder received material containing 15 billion organisms with diphtheria and tetanus toxoid. One of the babies showed marked diffuse slowing following the injection which disappeared after one week; another showed less marked slowing with fever as the only symptom. This study shows that mild, but possibly significant, cerebral reactions occur in addition to the reported very severe neurological changes.

The risk of serious neurological complications from pertussis is infinitely greater than the risk from preventive immunizations, so these injections should not be abandoned, but the material should be made safer.

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EXPERIMENTAL PRODUCTION OF THE PULMONARY HYALINE MEMBRANE SYNDROME

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THE triad of pathologic changes in the lungs of infants who die with the pulmonary hyaline membrane syndrome consists of atelectasis, vascular engorgement, and an eosinophilic hyaline-like membrane which lines alveolar ducts and alveoli. It was first completely described by Johnson and Meyer[1] in 1925 and two theories of its etiology have existed for many years, an exogenous theory which postulates that the membrane is derived from aspirated amniotic fluid and an endogenous theory which postulates its formation from a pulmonary exudate. The membrane has been produced experimentally by many workers[2] and may be found occasionally in human adults who die of a variety of diseases.

The accompanying atelectasis, however, would seem to be an integral component of the human syndrome. This was not produced experimentally, to our knowledge, until we created the triad in guinea pig lungs.[3] Confirming the work of Weiner and associates,[4] which demonstrated the thromboplastin-like activity of fresh amniotic fluid, we reasoned that both theories might be partially correct: aspirated amniotic fluid may speed the clotting of a pulmonary exudate and the syndrome may result. We used guinea pigs as the experimental animal, because of the similarity of guinea pig and human lungs. Human amniotic fluid and plasma were injected into the tracheas of live, adult guinea pigs. At various intervals postoperatively, the lungs were examined and three out of forty animals showed the complete pulmonary hyaline membrane syndrome. Because of complications of anesthesia, pulmonary edema, hemorrhage, and infection, and because of the low percentage of positive animals, a new set of experiments was designed. The present report records the results in eighty-seven study animals and 117 control animals.

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MATERIALS AND METHODS

Medium and large guinea pigs of either sex were used. The trachea was exposed through a midline neck incision and mobilized by a closed Kelly clamp which was inserted behind it. The experimental fluids were introduced directly into the trachea through a needle attached to a syringe. The skin incision was then closed. The procedure was simple, quick, and seemed relatively nontraumatic. All guinea pigs were locally anesthetized with 2 per cent aqueous procaine hydrochloride and each animal received, intramuscularly and immediately postoperatively, a solution containing 25,000 units penicillin, 75,000 units

procaine penicillin, and 0.125 Gm. dihydrostreptomycin. The animals were sacrificed with intraperitoneal sodium ethyl thiobarbiturate (Pentothal).

The human plasma was obtained from post-partum patients. It was oxalated and occasionally pooled lots were used. The human amniotic fluid was obtained by aspiration of the amniotic sac either at cesarean section or prior to elective amniotomy. The donors were selected at random. The fluids were administered fresh and at room temperature, or were deep-frozen and thawed immediately preceding injection. Some amniotic fluids were clear; others were clouded with varying amounts of vernix caseosa.

Study Series I.—Sixty-five guinea pigs received intratracheal injections of plasma and amniotic fluid, 1.0 to 1.5 ml. amounts of each. Twenty-six (40.0 per cent) died within thirty minutes and showed pulmonary edema.

Five (7.7 per cent) died in one to four hours; their lungs showed atelectasis, vascular engorgement, and edema. Thirty-four (52.3 per cent) were sacrificed five to seventy-two hours postoperatively; atelectasis, vascular engorgement, and edema were commonly found in their lungs and six of these animals showed the pulmonary hyaline membrane syndrome.

Study Series II.—Fifteen guinea pigs received intratracheal injections of plasma and amniotic fluid, 1.0 to 1.5 ml. amounts of each. The procedure was then repeated after intervals of three to seventy-two hours. Three (20.0 per cent) died at reoperation. The remaining twelve (80.0 per cent) were sacrificed six to forty-eight hours postoperatively and their lungs showed extensive atelectasis, vascular engorgement, and edema; three of them showed the pulmonary hyaline membrane syndrome.

Study Series III.—Seven guinea pigs received intratracheal injections of a mixture of one part of the sediment from centrifuged amniotic fluid diluted with four parts of plasma. Each animal received 2 ml. of this suspension which was thick and cheesy. Three (42.8 per cent) died within thirty minutes and their lungs showed edema, patchy atelectasis, and hemorrhage. Four (57.2 per cent) were sacrificed twenty-four hours postoperatively and showed similar lung pathology except that one of them showed the pulmonary hyaline membrane syndrome.

Control Series I.—Thirty-six guinea pigs received intratracheal injections of 1 to 4 ml. of cold (10° C.), normal saline. Sixteen (44.5 per cent) died within five minutes and were not autopsied. The remaining twenty (55.5 per cent) were sacrificed eighteen to forty-six hours postoperatively and their lungs showed patchy atelectasis, emphysema, and hemorrhage. None showed the pulmonary hyaline membrane syndrome. The animals averaged 646 grams in weight and their lungs averaged 5.0 grams.

Control Series II.—Thirty guinea pigs received intratracheal injections of 2 ml. of amniotic fluid. Three (10.0 per cent) died within thirty minutes and their lungs showed patchy atelectasis. Twenty-seven (90.0 per cent) were sacrificed twenty-four to forty-eight hours postoperatively and their lungs showed extensive atelectasis, intrabronchial plugs of basophilic epithelium, and vascular engorgement. The animals averaged 520 grams in weight and their lungs averaged 4.4

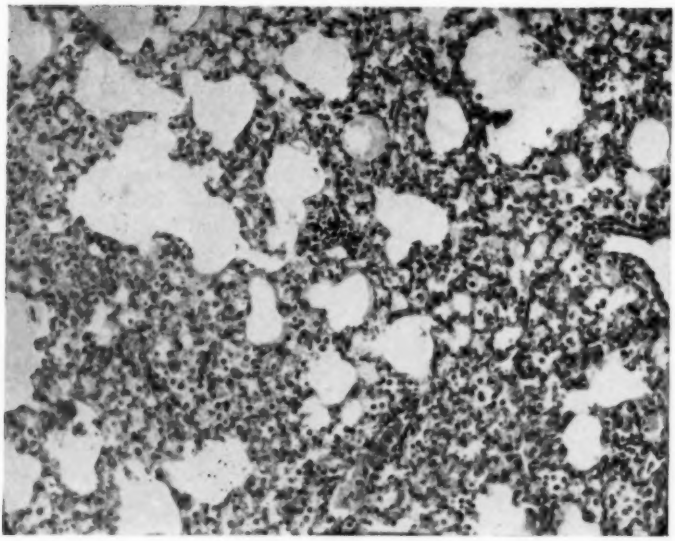

Fig. 1.—Photomicrograph of lung of guinea pig which received 2 ml. of amniotic fluid. It shows patchy atelectasis and occasional distended alveolar ducts and alveoli ringed with poorly staining eosinophilic material. (Hematoxylin and eosin stain; ×140; reduced ⅓.)

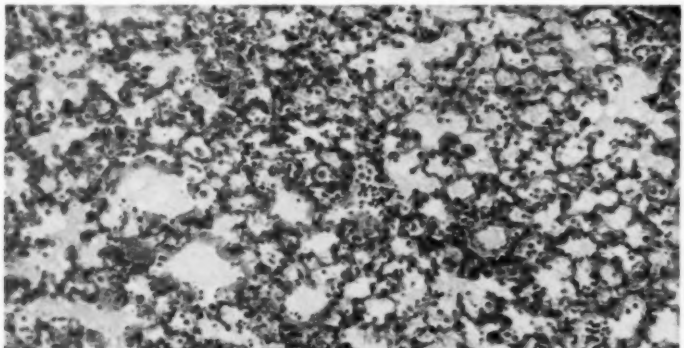

Fig. 2.—Photomicrograph of lung of guinea pig which received 1 ml. of plasma and 1 ml. of normal saline. It shows vascular engorgement, edema, and hyaline membrane. (Hematoxylin and eosin stain; ×140; reduced ⅓.)

grams. One animal died two hours postoperatively; it weighed 550 grams and the lungs weighed 7.5 grams. The latter showed patchy atelectasis and areas where alveolar ducts and alveoli were distended with edema and occasionally ringed with eosinophilic material. This appeared to be fluid. It and their lungs showed massive edema and hemorrhage. The animals averaged 481 grams in weight and their lungs averaged 5.4 grams. One animal died five hours postoperatively and its lungs showed massive edema and extensive hemorrhage; it weighed 550 grams and the lungs weighed 6.0

TABLE I. ANIMALS WITH PULMONARY HYALINE MEMBRANE SYNDROME

AMNIOTIC FLUID	PLASMA	POST-OPERATIVE SURVIVAL
1. 1.5 ml.—fresh clear—normal pregnancy	1.5. ml.—fresh 12 hr. post-partum	Sac. 24 hr.
2. 1 ml.—fresh clear—normal pregnancy	1 ml.—frozen pooled 24-72 hr. post-partum	Sac. 47 hr.
3. 1 ml.—fresh clear—normal pregnancy	1 ml.—frozen pooled 24-72 hr. post-partum	Sac. 47 hr.
4. 1 ml.—fresh clear—normal pregnancy	1 ml.—frozen pooled 24-72 hr. post-partum	Sac. 47 hr.
5. 1 ml.—fresh clear—normal pregnancy	1 ml.—frozen pooled 24-72 hr. post-partum	Sac. 47 hr.
6. 1 ml.—frozen clear—38 wk. induction for erythroblastosis	1 ml.—frozen pooled 48-72 hr. post-partum	Sac. 6 hr.
7. Fresh—heavy with vernix normal pregnancy	Fresh 48 hr. post-partum	Sac. 24 hr.
Comment: Received 2 ml. of mixture of one part concentrated amniotic fluid sediment with four parts plasma.		
8. 1.25 ml.—frozen clear—normal pregnancy	1.25 ml.—fresh 72 hr. post-partum	
Comment: Reoperated after 70 hr. and received 1 ml. frozen 39 wk. elective section amniotic fluid plus 1 ml. frozen 72 hr. post-partum plasma. Sacrificed 22 hr. after reoperation.		
9. 1 ml.—fresh clear—35 wk. section for premature separation	1 ml.—fresh normal post-partum	
Comment: Reoperated after 24 hr. and received 1 ml. frozen term elective section amniotic fluid plus 1 ml. frozen 32 wk. section plasma. Sacrificed 48 hr. after reoperation.		
10. 1 ml.—fresh clear—35 wk. section for premature separation	1 ml.—frozen normal post-partum	
Comment: Reoperated after 24 hr. and received 1 ml. fresh 38 wk. induction (for erythroblastosis) amniotic fluid plus 1 ml. frozen normal post-partum plasma. Died 24 hr. after operation.		

stained poorly with hematoxylin and eosin, and with the periodic acid-Schiff stain which colored the hyaline membranes of ten positive animals, and of several human subjects, a vivid purple. (Fig. 1.)

Control Series III.—Twelve guinea pigs received intratracheal injections of 1 to 2 ml. of plasma. Ten (83.4 per cent) died within thirty minutes grams. Another animal was sacrificed twenty-four hours postoperatively and its lungs showed even more marked edema and hemorrhage; it weighed 475 grams and the lungs weighed 13.0 grams. No animals showed the pulmonary hyaline membrane syndrome.

Control Series IV.—Thirty-nine guinea pigs received intratracheal injections of a mixture of 1 ml. of

plasma and 1 ml. of normal saline. Seventeen (43.6 per cent) died within thirty minutes and showed heavy, red lungs with edema and hemorrhage. They averaged 480 grams in weight and their lungs averaged 5.6 grams.

Five (12.8 per cent) died in one to two hours, and the remaining seventeen (43.6 per cent) were sacrificed twenty-four to forty-eight hours postoperatively. Their lungs were heavy and red and showed edema and hemorrhage. The animals averaged 538 grams in weight and their lungs averaged 5.9 grams. One of them, sacrificed forty-eight hours postoperatively, showed lungs with vascular engorgement, marked edema, and occasional alveolar ducts and alveoli which were lined with an eosinophilic hyaline membrane; there was no atelectasis. Although it weighed only 430 grams, its lungs weighed 7.0 grams. (Fig. 2.)

ANIMALS WITH PULMONARY HYALINE MEMBRANE SYNDROME

Ten (11.5 per cent) of the eighty-seven animals in the study series developed the pulmonary hyaline membrane syndrome. Table I lists these animals, the types and amounts of fluids injected, and the survival times.

No single specimen of amniotic fluid or plasma produced consistent results and the amount of vernix in the amniotic fluid did not seem to be significant. Dyspnea and retraction of the thoracic cage appeared several hours before death in all of the ten animals.

On gross inspection, the lungs were firm and deep red. There were scattered, small aerated areas, but the specimens all sank in formalin solution. All lung sections showed a slight, diffuse infiltration of polymorphonuclear leukocytes.

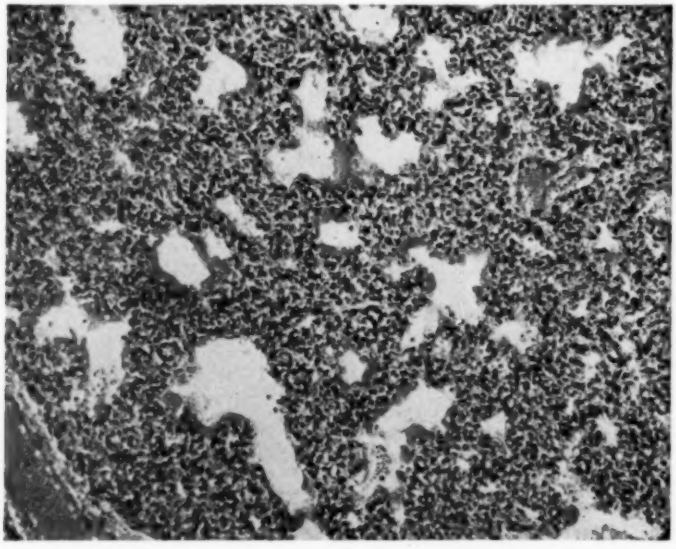

Fig. 3.—Photomicrograph of lung of human infant who died with the pulmonary hyaline membrane syndrome. (Hematoxylin and eosin stain; ×140; reduced ⅙.)

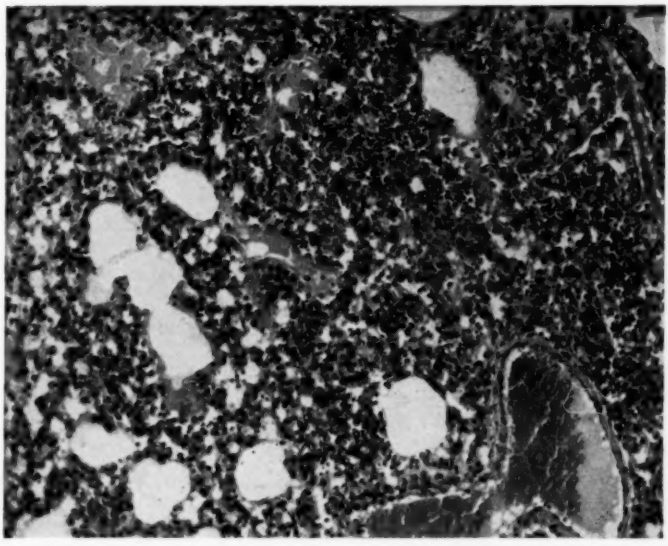

Fig. 4.—Photomicrograph of lung of guinea pig which received 1 ml. each of plasma and amniotic fluid. It shows atelectasis, vascular engorgement and hyaline membrane. (Hematoxylin and eosin stain; ×140; reduced ⅕.)

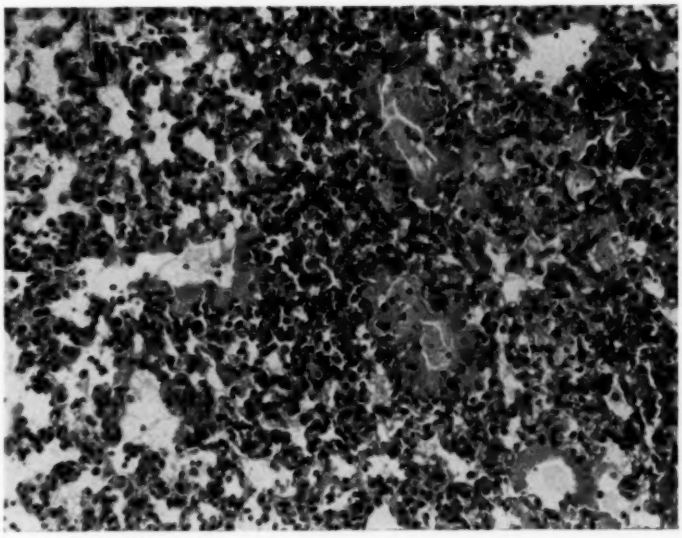

Fig. 5.—Photomicrograph of lung of guinea pig which received 1 ml. each of plasma and amniotic fluid. It shows atelectasis, vascular engorgement, and hyaline membrane. (Hematoxylin and eosin stain; ×200; reduced ⅕.)

Fig. 3 is a section of the lungs of a human infant, who was born by vaginal delivery after 34 weeks' gestation and who died with the pulmonary hyaline membrane syndrome.

Figs. 4 and 5 are sections of the lungs of study animals. They are representative of the ten animals and show extensive atelectasis, vascular engorgement, and eosinophilic hyaline membrane which lines occasional dilated alveolar ducts and alveoli.

DISCUSSION

The pulmonary hyaline membrane syndromes which were produced in these experiments resembled the human disease both clinically and on gross and microscopic examination. It may be significant that guinea pigs, with their vascular lungs and unusual bronchiolar musculature, were used as the experimental animals.

Fresh, or deep frozen and thawed, human amniotic fluid, with or without excessive vernix caseosa, irritates the lungs of the adult guinea pig and causes extensive atelectasis. De and Anderson[5] have recently produced the complete syndrome in *newborn* guinea pigs merely by irritating their lungs with 90 to 95 per cent oxygen, but no extensive atelectasis resulted in the present series unless amniotic fluid was used. It is possible that amniotic fluid, aspirated in excessive amounts, is etiologically important in the production of the atelectasis of the human disease. In this connection, it is pertinent to note that careful observation of those infants who later succumb with the syndrome usually reveals a period of respiratory distress immediately after birth.

Human plasma, introduced into the lungs of the adult guinea pig, produces hemorrhage, massive edema, and a high mortality. Even when it is diluted with normal saline, it still produces considerable pulmonary edema.

In the present experiments, it appears that the injected plasma caused an intrapulmonary exudation of fluid. This was so massive, in one control animal, that the exudate formed a membrane although no atelectasis was present. Generally, however, amniotic fluid was necessary, in addition to plasma, to create atelectasis and a membrane. It seems reasonable to suggest that the thromboplastin-like activity of the amniotic fluid aided in clotting the pulmonary exudate.

It is possible that the pulmonary hyaline membrane syndrome may result in the human infant when aspirated amniotic fluid mixes with pulmonary exudate. The amniotic fluid may create massive atelectasis and may speed the clotting of the exudate to form a membrane. The etiologies of the exudate may well be diverse—for instance, pulmonary irritation from the amniotic fluid itself or from the inhalation of high concentrations of oxygen,[5, 6] vagus nerve injury,[7] high progesterone environment of the premature infant,[6, 8] or left-sided cardiac failure. If the exudate is sufficiently extensive, as in terminal rheumatic heart disease, in the plasma control animal, or in the oxygen experiments previously cited,[5, 6] it may form a membrane unaided by amniotic fluid. The possibility of exudation into the lungs of the newborn infant would seem to be enhanced by the increased vascularity of these organs. Most newborn infants unavoidably aspirate amniotic fluid, and it is suggested that future work on the pathogenesis of the human syndrome should en-

deavor to elucidate the etiologies of pulmonary edema in the neonatal period.

SUMMARY

Eighty-seven adult guinea pigs received intratracheal injections of a mixture of human amniotic fluid and human plasma. Ten of them developed the thoracic retraction which is seen in newborn infants who have the pulmonary hyaline membrane syndrome, and post-mortem examination of their lungs revealed findings similar to those in the human disease. The lungs were firm, deep red, and sank in formalin solution; they showed extensive atelectasis, vascular engorgement, and eosinophilic hyaline membrane which lined occasional dilated aveolar ducts and alveoli.

One hundred seventeen control animals received intratracheal injections of human amniotic fluid, human plasma, or cold normal saline. In general, the amniotic fluid produced extensive atelectasis and pulmonary vascular engorgement; the plasma produced pulmonary edema and hemorrhage and, in one animal, scattered areas of eosinophilic hyaline membrane without accompanying atelectasis; the saline produced patchy atelectasis, emphysema, and hemorrhage.

The present experiments suggest that the injected plasma caused an intrapulmonary exudation of fluid and pulmonary vascular engorgement. The injected amniotic fluid created atelectasis. Its thromboplastin-like activity may have aided in clotting the exudate to form a membrane although one animal accomplished this with massive pulmonary edema due to plasma alone.

It is suggested that the pulmonary hyaline membrane syndrome in the human infant may be the result of a similar mechanism when aspirated amniotic fluid mixes with a pulmonary exudate. The etiologies of the exudate are probably diverse and future investigation into the pathogenesis of the human syndrome might well endeavor to elucidate the etiologies of pulmonary edema in the neonatal period.

We thank Dr. John C. Henthorne for his assistance in the interpretation of the pathologic material.

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THE PREPUBERAL DIAGNOSIS OF OVARIAN AGENESIS AND ITS RELATIONSHIP TO STATUS BONNEVIE-ULLRICH

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TURNER[1] in 1938 described seven young women who presented the clinical triad of sexual infantilism, congenital webbed neck, and cubitus valgus, a syndrome to which his name was appended. Later investigators[2, 3, 4, 5, 6] collected a number of closely related cases with sexual infantilism in association with short stature and one or more cardiovascular, bony, ocular, and renal anomalies. The name "ovarian agenesis" was applied to this syndrome. Webbing of the neck as described by Turner was an infrequent finding and his series of cases was thought to be a subgroup of the syndrome of ovarian agenesis.[2] Other investigators found a higher incidence of congenital webbed neck and cubitus valgus associated with ovarian agenesis[7, 8, 9]; these more closely resembled Turner's original series. Turner[10] stated that one-third to one-half of cases of primary hypogonadism in the female have webbing of the neck and, conversely, hypogonadism is present in one-third of females with webbing of the neck. Neither "Turner's syndrome" nor "ovarian agenesis" adequately describes the true nature of this syndrome. Other names such as "congenitally aplastic ovaries" or "primary-hypo-ovarianism" are equally inappropriate. For purposes of this discussion, however, the name "ovarian agenesis" will be used since it appears to be most widely accepted.

Hormonal excretion studies in these patients reveal subnormal levels of urinary estrogen, diminished urinary excretion of 17-ketosteroids, and high levels of urinary gonadotropins. The sexual infantilism is thought to be due to a primary failure of the ovaries to develop, and the high excretion of gonadotropins is thought to be due to the failure of the ovarian hormones to exert their repressing effect on the pituitary gland. Diagnostic laparotomies performed on these patients do not reveal any structure resembling a mature ovary.[4] The ovaries are represented by glistening white streaks approximately 3 mm. in width, located on the posterior surfaces of the broad ligaments. Microscopic examination reveals no evidence of germinal epithelium or ovarian follicles.

Many of the features of the syndrome of ovarian agenesis can obviously be explained on the basis of lack of ovarian hormones but the presence of short stature and the high incidence of multiple congenital anomalies suggest the probability that these are linked genetic defects. The essential features of the syndrome have recently been reviewed by Jackson[9]: I. Gonadal agenesis: (A) Primary lack of ovarian development as proved by laparotomy;

From The Georgetown University Medical Center, Department of Pediatrics, and The Children's Hospital.

(B) Secondary: primary amenorrhea, infantile uterus and vagina, mammary hypoplasia with pin-point nipples, and scanty pubic and axillary hair; normal or slightly retarded bone age with mild generalized osteoporosis; increased urinary gonadotropins and frequently diminished urinary 17-ketosteroid excretion. II. Skeletal defects: short stature with an adult height averaging about 55 inches, a "shield-like" chest (broad and stocky with wide-spaced nipples), a span which is often wider than the height, and minor vertebral chondrodystrophy ("epiphysitis"); webbed neck and cubitus valgus are commonly but not invariably present. III. Associated anomalies which may include ocular defects such as squint, ptosis or cataract, cardiovascular defects such as coarctation of the aorta or hypertension independent of coarctation, mental retardation or deaf mutism. A detailed list of anomalies is included in Table I. Urinary follicle-stimulating hormone (FSH) determinations in these patients give values ranging from 192 to 576 mouse units per day as compared with 10 to 50 mouse units per day in normal adult females; 17-ketosteroid excretion is usually 3 to 6 mg. per day as compared with 5 to 14 mg. per day in normal adult females.

It will be apparent that the lack of ovarian hormones in the female will not become evident until the time of puberty. Consequently, the majority of reported cases of ovarian agenesis have been diagnosed following puberty. As the other clinical manifestations of this syndrome have become more widely recognized, however, scattered reports in prepuberal females have appeared in the literature. Final confirmation in the absence of laparotomy will need to await the onset of puberty in these children. Turner[10] has reported a 5½-month-old female who was undersized and presented soft tissue webbing of the neck, hypoplastic mandible, congenital heart disease, pit-

TABLE I. CLINICAL FEATURES OF THE SYNDROME OF OVARIAN AGENESIS[1-12]

I. Gonadal Agenesis	II. Skeletal Defects	III. Associated Anomalies
Primary amenorrhea	Short (but not dwarfed) stature	Ocular defects
Infantile uterus and vagina	Webbed neck	Bilateral ptosis
Mammary hypoplasia	Cubitus valgus	Tubular vision
Pin-point nipples	"Shieldlike" chest	Bilateral cataract
Scanty pubic and axillary hair	Wide span	Mild exophthalmus
Normal or slightly retarded bone age	Pes cavus	Retinal albinism
Mild generalized osteoporosis	Minor vertebral chondrodystrophy ("epiphysitis")	Strabismus
Late epiphyseal union	Spina bifida	Coloboma
Increased urinary gonadotropins	Madelung's deformity	Mental retardation
Diminished urinary 17-ketosteroids	Fusion of cervical vertebrae	Congenital deafness
	Abnormal rib development	Vascular anomalies
	Shortened phalanges	Coarctation of aorta
	Hypoplasia of mandible	Hypertension of unexplained origin
	Highly arched palate	Renal anomalies
	Short neck	Azygos lobe of lung
	Asymmetry of gums	Lymphangiectatic edema
	Syndactylism	Telangiectases and nevi
	Osteogenesis imperfecta tarda	
	Abnormal epiphyses	

ting edema of the legs and feet, and hypertrophy of the fourth digit of the left hand. Wilkins[11] states that it is improbable that there will be an elevated excretion of FSH in cases of ovarian agenesis prior to the age of 10 to 12 years when secretion of pituitary gonadotropins first begins. He reported a 3-year-old female who was dwarfed and had a webbed neck and coaretation of the aorta. FSH was absent in the urine, but laparotomy confirmed the diagnosis of ovarian agenesis. Lisser and associates[8] give 0 to 5 mouse units as a normal twenty-four-hour FSH excretion in premenarchial females. Silver and Kemp[12] have reported two cases of ovarian agenesis diagnosed at 2½ years and 8 years 10 months, respectively. The urinary gonadotropin level was elevated above 5 mouse units in both instances, but this is the only published report of elevated FSH excretion in premenarchial females.

Primary gonadal agenesis has also been reported in the male. James[13] in 1952 collected five cases from the literature and added a sixth of his own. Salient clinical features include webbed neck, short stature, hypoplastic testes, cubitus valgus, and mental retardation plus other skeletal, ocular, and cardiac anomalies. The syndrome is not so clearly delineated in the male, but testicular biopsy has confirmed the diagnosis in at least one instance. Biopsy revealed hypoplasia of the seminiferous tubules, azoospermia, and an increase in interstitial cells.[13] Despite testicular hypoplasia, the penis is usually of normal size. Four of the six males were under 10 years of age, and the presence of webbed neck usually called attention to the syndrome. 17-Ketosteroid and gonadotropin excretion determinations when performed were within normal limits.

Ullrich[14] in 1930 described a combination of multiple malformations in a group of nineteen patients with soft tissue webbing of the neck or peripheral joints, cranial nerve dysfunction, muscular aplasias, and lymphangiectatic edema of the hands and feet. These were associated less frequently with breast hypoplasia, dwarfism, and skeletal anomalies. In attempting to explain the origin of these congenital malformations, he later proposed a theory based on experimental work performed in mouse embryo and described by Bonnevie.[15] This syndrome subsequently became known as "status Bonnevie-Ullrich." As more cases were reported, the syndrome became better defined and was described in its present form by Rossi[16] in 1945. The four cardinal signs as described by Rossi were (1) "pterygium"—soft tissue webbing of the neck; (2) lymphangiectatic edema of the hands and feet; (3) mental retardation, and (4) cutis laxa. Table II contains a complete list of the features of the syndrome. Rossi also called attention to several "formes frustes" patients who did not present all the cardinal signs but had many of the secondary findings. Rossi and Caflisch[17] in 1951 reviewed the literature and added several additional features to the syndrome. Many of the patients described by Rossi were prepuberal and a number of these were recognized during the first year of life.

The "pterygium" (webbing of skin and connective tissue of the neck) is the most prominent sign of status Bonnevie-Ullrich. It is bilateral and symmetrical and frequently exerts traction

on the corners of the mouth, causing a downward droop and "sphinxlike" visage. There is a frequently associated low insertion of the ears. The pterygium while almost always present may be absent in the presence of all the other characteristics of the syndrome.[17]

Mental retardation is quite common. It is a peculiar type of mental retardation, however, in that as these children grow older, many seem to "catch up" and eventually have normal or near-normal intelligence.[17] The lymphangiectatic edema of the hands and feet is present at birth and has been proved by histopathologic investigation to be due to dilatation of lymphatic capillaries. The edema is nonpitting and is confined to the neck and dorsal surfaces of the hands and feet. Resorption of this edema practically always occurs during the first two years of life, leading to cutis laxa or hyperelastica in the areas which were formerly edematous. The cutis laxa may also be generalized. Short stature is a regular feature of the syndrome and the reduction of height is proportional. These children are short from birth and the short stature is frequently noted during the first year of life.

One of the most interesting findings is the frequent appearance of convolutional markings or "digitalization" of the skull as seen by x-ray. This is a frequent finding in craniostenosis, but in status Bonnevie-Ullrich the sutures are normal and there is no other collateral evidence of increased intracranial pressure. It has been proposed that this abnormal roentgenographic finding results from increased intracranial pressure during fetal life.[17] The only other frequently described radiographic abnormality is a "mushroomlike formation" of the epiphyses of the long bones.

Rossi and Caflisch[17] give no exact incidence of cardiac malformations but state that these anomalies are much more common in patients with a pterygium. They mention interventricular septal defects and coaretation of the aorta as being the most common defects. Pulmonary malformations were noted in two instances. One patient had a congenital lung cyst and another an accessory lobe of the lung.

TABLE II. CLINICAL FEATURES OF STATUS BONNEVIE-ULLRICH
(Rossi, 1945; Rossi and Caflisch, 1951)

Cardinal Signs
*1. Pterygium colli (bilateral soft tissue webbing of the neck)
*2. Mental retardation
*3. Lymphangiectatic edema of hands and feet[11]
*4. Cutis laxa and hyperelastica[14]
Associated Signs
5. "Ogival" (high-arched) palate
6. Adherent ear lobes
7. Skeletal anomalies: "mushroom-shaped" epiphyses of long bones
*8. Muscular hypoplasia[14]
9. Epicanthus with hyperteliorism
10. "Digitalization" of the skull (prominent convolutional markings)
*11. Small stature, frequently noted during the first year of life
*12. Cranial nerve abnormalities—III, IV, VI, VII cranial nerves[1, 3, 5]
*13. Mammary hypoplasia
14. Nail dystrophy
*15. Deformities of the extremities—syndactyly, clubfoot[6, 14]
16. Skull abnormalities—asymmetry of the skull and facial bones
*17. Mandible hypoplasia[5, 10]
*18. Telangiectases
*19. Increased joint mobility[14]
*20. Thorax deformity[14]

*Signs which are shared by status Bonnevie-Ullrich and the syndrome of ovarian agenesis. References refer to the occurrence of the abnormality in reported cases of gonadal agenesis.

Certain resemblances between status Bonnevie-Ullrich and the syndrome of ovarian agenesis are readily apparent (Table II). Little investigation of

ovarian function has been performed in cases of status Bonnevie-Ullrich, although mammary hypoplasia has been described consistently in postpuberal females. Rossi[16] described a case of status Bonnevie-Ullrich in a young girl first diagnosed at age 5 months and observed regularly until the age of 22 years. At the latter age she had not menstruated, had scanty axillary and pubic hair, and no demonstrable breast tissue. Many other European authors have noted the similarity between status Bonnevie-Ullrich and the "syndrome of Turner." Baggio[18] described a 10-year-old female with the typical features of status Bonnevie-Ullrich (pterygium of the neck, lymphangiectatic edema of the dorsal surfaces of the hands and feet, short stature, high-arched palate, digital skull markings) evident since birth. Urinary gonadotropin determinations on several occasions at age 10 ranged from 25 to 40 mouse units.

We have recently studied two patients who present many of the features of these two syndromes. The first is a 2-year-old white female who appears to be a case of status Bonnevie-Ullrich. The second is a 10-year-old Negro female who more nearly resembles an example of the syndrome of ovarian agenesis.

CASE REPORTS

CASE 1.—S. A., a 27-month-old white female, was admitted to the pediatric service of Georgetown University Hospital on April 27, 1954, for evaluation of failure to develop normally and for a peculiar facial appearance. She was born two months prematurely and weighed 4 pounds 5 ounces. The pregnancy was uneventful and delivery was uncomplicated but occurred in a taxi on the way to the hospital. The child was noted to have edema of the dorsal surfaces of the hands and feet at birth but otherwise did very well and was discharged from the hospital at the age of 2 weeks. During the first year of life she had multiple severe episodes of diarrhea attributed to food allergy. Various dietary regimes were tried and in the year prior to admission she had been placed on a diet of meat-base formula and certain puréed

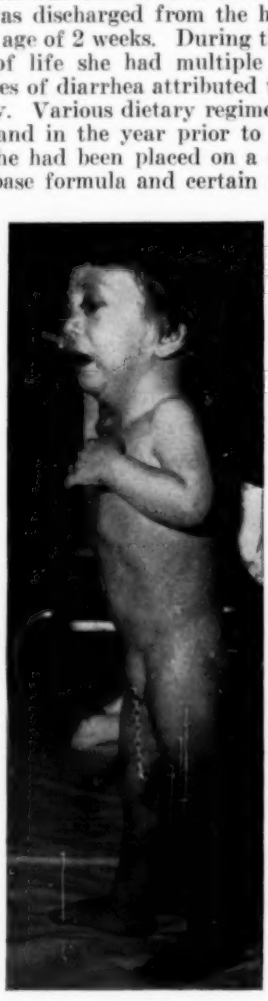

FIG. 1.—Note the relatively large head with mild proptosis of the eyes. Case 1.

fruits and vegetables. Despite her diarrheal episodes she had always had a vigorous appetite. Six months prior to admission (at 20 months of age) she weighed only 15 pounds. At that time she was placed in a convalescent home where she was given a regular

diet for her age. She tolerated all foods well, had no diarrhea, and gained three pounds in three months.

The child had developed slowly, sat up at one year of age and walked around chairs at 22 months. She walked at 24 months of age unassisted. Her vocabulary consisted of "hi" and "bye-bye." Teeth erupted at 2 months but this had also occurred in her older siblings. The edema of the dorsal surfaces of the hands and feet had gradually lessened until at the time of the present hospital admission only the fingers were involved. Two older siblings, a sister aged 6 years and a brother aged 4 years, are normal in all respects. There is no parental consanguinity.

Physical examination revealed a small, undernourished white female

Fig. 2.—Laxity of the skin and of the neck. Case 1.

with a relatively large head and protuberant eyes (Fig. 1). Her weight was 21 pounds.

Head circumference was 46.5 cm. (18⅜ in.), chest circumference 46.5 cm. (18⅜ in.), abdominal circumference 44.5 cm. (17⅝ in.). Height was 80 cm. (32 in.), lower body segment 34 cm. (13⅜ in.), and upper body segment 46 cm. (18⅛ in.).

Her head appeared enlarged. The fontanels and sutures were closed. There was bilateral mild proptosis of the eyes with bilateral epicanthus. Interpupillary diameter was 47 mm. (normal 45 to 53 mm.). There were hypoplasia of the mandible and a highly arched palate. The neck was short, and although there was no true webbing, the skin of the side of the neck was very lax (Fig. 2). There was no deformity of the thorax. The lungs were clear. The heart was normal. Blood pressures revealed: RA 85/50, LA 88/50, RL 114/60, LL 104/65. The femoral pulsations were good. The abdomen was protuberant but was otherwise normal. Her fingers were short and stubby and there was nonpitting edema of all the second phalanges (Fig. 3). The skin of the dorsal surfaces of the hand was velvety to the touch. Muscular development was normal.

Blood and urine examinations were normal. Determinations of the blood urea nitrogen, fasting blood sugar,

Fig. 3.—Lymphangiectatic edema of the second phalanges. Case 1.

carbon dioxide combining power, serum chloride, serum sodium and serum potassium, total protein and albumin-globulin ratio, calcium, phosphorus, alkaline phosphatase and cholesterol were all normal. A glucose tolerance test was normal. There was no abnormal amount of fat or starch in the stool. Stool trypsin was present in normal amounts. X-rays of the skull revealed a marked convolutional pattern (Fig. 4). The fontanels and sutures were closed but not synostosed. The sella turcica was normal. There

was asymmetry of the skull with the right side slightly smaller than the left, especially in the posterior fossa region. There was also asymmetry of the orbits and facial bones. The bone age was consistent with that of a child of 9 to 12 months of age. X-rays of the lower extremities revealed transverse lines in the distal metaphyses of the femora suggestive of growth disturbance. Intravenous pyelogram was normal. An electrocardiogram was within normal limits. An electroencephalogram was reported abnormal with a bilateral temporal focus. Psychometric examination at age 24 months revealed a performance level of 15½ months with a test range of 12 to 20 months.

The hospital course was uneventful. The patient ate well, had normal bowel movements, and gained weight. She was discharged to be followed in the outpatient department of the endocrine clinic.

Comment.—Certain features of status Bonnevie-Ullrich were found to be present in this child: lymphangiectatic edema of the second phalanges, mild mental retardation, short stature with a relatively large head, bilateral epicanthus and mild exophthalmus, high-arched "ogival" palate, asymmetry of the skull and facial bones, hypoplasia of the mandible, and increased convolutional markings of the skull. No true pterygium was present but the skin of the side of the neck was very lax. While many of the congenital malformations presented by this child may be found singly or in combination in other clinical syndromes, we feel enough characteristics are present to describe this as a "forme fruste" example of status Bonnevie-Ullrich.

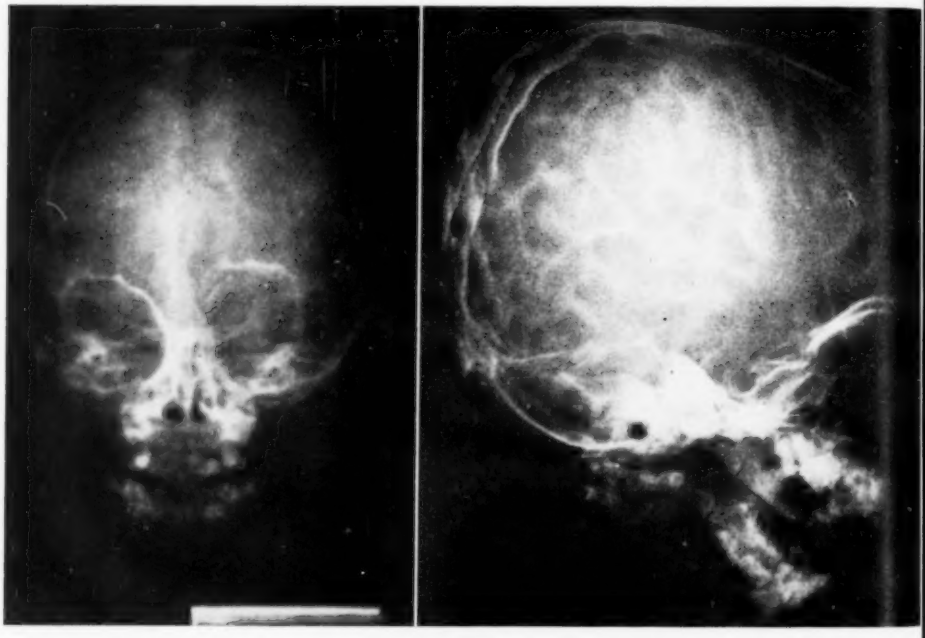

Fig. 4.—"Digitalization" of the skull. Note that the suture lines are still clearly visible. There is asymmetry of the orbital cavities and hypoplasia of the mandible. Case 1.

Case 2.—C. S., a 10-year-11-month-old Negro female, was admitted to the Children's Hospital on Sept. 13, 1954,

for investigation as a probable case of ovarian agenesis.

She was the fourth of ten children and was born at home with a physician in attendance. The mother's pregnancy was uneventful. Delivery was uncomplicated and her neonatal course uneventful. Birth weight was 5 pounds. At age 6 months she was hospitalized at the Children's Hospital with bronchopneumonia. During the

Fig. 5*A*.

hospitalization a loud systolic murmur which was heard over the entire precordium was noted. Roentgenographic examination of the chest revealed a "boot-shaped" heart, and a diagnosis of congenital heart disease of undetermined etiology was considered. No other physical abnormalities were recorded at that time. At age 9 months she was rehospitalized with an episode of diarrhea and vomiting. The cardiac findings were confirmed, but no attempt was made to further investigate the type of congenital heart disease. The patient was noted to have a large head and a bulging anterior fontanele, and a diagnosis of hydrocephalus was considered. Pneumoencephalogram revealed the ventricular system to be somewhat dilated and this was thought to be indicative of mild hydrocephalus. She was hospitalized for the third time at age 16 months with another

Fig. 5*B*.

Fig. 5*A* and *B*.—Short stature, bilateral webbing of the neck, "sphinxlike" visage, epicanthus with hyperteliorism, and hypoplastic mandible. Case 2.

episode of bronchopneumonia. The head enlargment was again commented upon, but no mention was made of any additional abnormalities.

The child was followed sporadically in the Children's Hospital cardiac clinic over the intervening years, but due to frequently broken appointments, an adequate cardiac investigation was never performed. Several investigators had suggested the diagnosis of patent ductus arteriosus or a septal defect. There was never any evidence of cyanosis or congestive heart failure. She was lost to observation during the six years immediately preceding the present hospital admission.

Despite a good appetite the child was always noted to be short and underweight for her age. She sat up at one year of age and walked at age 4. She said a few words at age 2 but her speech development had always been slow. She had never attended school after being sent home because of her obvious mental retardation. No attempt was ever made to ensure special schooling.

The patient has four full siblings and five half-siblings. There was no parental consanguinity. The only other developmental anomaly noted in the family was the presence of unilateral ptosis in one half-brother.

Just prior to the present hospital admission, she returned to cardiac clinic when for the first time an obvious bilateral webbed neck was noted, and she was referred for hospitalization with a possible diagnosis of ovarian agenesis.

Physical examination on admission revealed a short, poorly developed Negro female with a relatively large head and obvious bilateral webbed neck involving skin and subcutaneous tissue (Fig. 5). Her weight was 43 pounds.

Head circumference was 54 cm. (21¼ in.), chest circumference 55 cm. (21½ in.), and abdomen circumference, 52 cm. (20¾ in.). Standing height was 121 cm. (47¾ in.), span 112 cm. (44¼ in.), upper body segment 60 cm. (23¾ in.), and lower body segment 61 cm. (24 in.).

The head was enlarged in the vertical diameter. Bilateral epicanthus was present together with an interpupillary distance of 60 mm. (normal 53 to 58 mm.). There was a divergent strabismus of 30 to 45 prism diopters. Vision in the right eye was 20/60; in the left eye the best corrected vision was finger counting at three feet. The ears appeared to be implanted lower than normal. The bridge of the nose was broad and flat, and breathing was primarily by mouth. The teeth were in excellent condition. The palate was highly arched. The mandible appeared hypoplastic.

Soft tissue webbing of the neck was present bilaterally but movement in all directions was unrestricted. There was no thorax deformity. There was no demonstrable breast tissue. The lungs were clear. The heart was enlarged to the left and a harsh "machinery-type" murmur was heard best in the second left intercostal space. Blood pressure determinations revealed RA 110/70, LA 110/70, RL 130/70, LL 130/70. Femoral pulsations were normal.

Abdominal examination revealed no abnormalities. The external genitals were normal but there was no axillary or pubic hair. The musculature of all extremities was hypoplastic and flabby.

Fig. 6.—Cutis laxa. Case 2.

The wrist joints were hyperextensible. Marked cutis laxa was present in all four extremities (Fig. 6). Pes cavus was present bilaterally. There were no digital deformities. The carrying angle of her arms was 160 degrees (normal female, 160 degrees; normal male, 170 degrees).

Blood and urine examinations were normal. An electrocardiogram was suggestive of an abnormal heart. An electroencephalogram was reported abnormal with a right parietal focus. Psychometric examination revealed an IQ of 49 and her mental age was placed at between 5 and 6 years.

Roentgenographic examination revealed a slightly asymmetrical skull which was otherwise normal. Exami-

nation of the chest revealed a "boot-shaped" heart which was enlarged to the left. The cervical spine was normal. Examination of the long bones of the extremities revealed a moderate generalized decalcification. The bone age was reported as normal. A considerable hypoplasia of the musculature and subcutaneous tissue was noted. Intravenous pyelogram was normal except for some evidence of mild pyelectasis.

The hospital course was uneventful and the patient was discharged to be followed in the cardiac and endocrine clinics. Arrangements have been made for special schooling. Two twenty-four-hour urine specimens collected for FSH determinations revealed values of 30 to 40 mouse units.

Comment.—This child would probably have been readily recognized as a case of ovarian agenesis by any investigator familiar with the clinical picture. Several additional features are present in this patient which have heretofore not received emphasis in case reports. Present in this case were short stature with a relatively large head and hypoplasia of the mandible, epicanthus with hyperteliorism, strabismus, high palate, moderate mental retardation, bilateral soft tissue webbing of the neck, congenital heart disease, cutis laxa, generalized hypoplastic musculature and joint hypermobility, and pes planus. It is debatable whether 30 to 40 mouse units in a female of this age represents an elevated value for FSH excretion.

DISCUSSION

It will be readily noted that most of the features in Case 2, a probable prepuberal example of ovarian agenesis, have been described in status Bonnevie-Ullrich. It is believed that the clinical abnormalities present in these two children serve to more closely relate the syndrome of ovarian agenesis and status Bonnevie-Ullrich. References to status Bonnevie-Ullrich in the American literature have been confined to sporadic mention of the entity. Potter[19] has described two newborn infants with nonpitting edema of the lower extremities associated with large folds of skin at the back of the neck. Autopsy of one of these infants revealed endomyocardial fibrosis and ovarian hypoplasia. With the increasing number of cases of ovarian agenesis in children being reported in the English and American literature it is felt that more of the signs of status Bonnevie-Ullrich will eventually be described in subsequent case reports of ovarian agenesis. Early diagnosis in these cases will serve to alert the parents to the possibility of the appearance of the signs of ovarian agenesis at the time of puberty. In the presence of the numerous other abnormalities characteristic of these two syndromes, it is felt that the diagnosis need not depend on the presence of congenital webbed neck and may be strongly suspected even without confirmatory laparotomy.

Ullrich[20] stated in 1950, "The typical complex abnormalities with pterygium colli described by me in 1932 as the 'symmetric form of Status Bonnevie-Ullrich' is identical with the 'syndrome of infantilism, webbed neck, and cubitus valgus' described by Turner in 1938." Rossi has suggested the name "Bonnevie-Ullrich-Turner syndrome." Whether or not this new designation gains universal acceptance, it certainly serves to call attention to a definite clinical picture and should result in the discovery of many more new cases of ovarian agenesis in children. Following is a list of what is believed to be the more frequently occurring clinical features of this syndrome in prepuberal children.

1. Congenital webbed neck.
2. Lymphangiectatic edema of the hands and feet.
3. Cutis laxa.
4. Short stature with relatively large head.
5. Mental retardation.
6. Epicanthus, hyperteliorism, high-arched palate.
7. Prominent convolutional markings of the skull.
8. Cardiac anomalies.
9. Hypoplastic musculature with joint hypermobility.
10. Skeletal anomalies.

In 1951, Rossi and Caflisch[17] reviewed a total of 197 cases of multiple malformations associated with pterygium formation and suggested the name "pterygium syndrome." They divided this syndrome into five subgroups: (1) bilateral Ullrich syndrome, as described in Table II; (2) dystrophia brevicolli congenita (Nielson): bilateral or unilateral pteryguim of the neck associated with malformations of the cervical vertebrae (Klippel-Feil) and one or more of the findings in Table II; (3) Turner's syndrome: bilateral webbing of the neck, hypogonadism, predilection for the female, and one or more of the findings in Table II; (4) unilateral status Ullrich: unilateral or asymmetric pterygium, especially of the extremities, with hypoplasia of the musculature of the involved extremity, predilection for the male, plus additional findings from Table II; (5) pterygoarthromyodysplasia congenita (arthrogryposis multiplex congenita): pterygium of the extremities, almost always asymmetrical or unilateral, aplasia of the musculature usually associated with displacement of the muscle insertions, ankylosis of the joints, and additional findings from Table II. Sixty-eight, or one-third of these 197 cases, demonstrated "infantilism of the Turner type." Twelve of these were "pure" ovarian agenesis and there were three "mild" cases in the male.

The foregoing classification is thought by Rossi and Caflisch to represent different variations of the same syndrome of defective development. Since all these syndromes are felt to include a series of variable factors, it is not surprising that clinically uniform results will not always be produced.

SUMMARY AND CONCLUSION

An attempt has been made to correlate the syndromes of ovarian agenesis of the American literature with status Bonnevie-Ullrich of the European literature. These syndromes are believed to be closely related. The syndrome of ovarian agenesis has been described primarily following the time of puberty, while status Bonnevie-Ullrich has been described mainly in children. A probable "forme fruste" case of status Bonnevie-Ullrich without pterygium has been described in a 2-year-old white female and compared with a probable case of ovarian agenesis in a 10-year-old Negro female. It is felt that familiarity with status Bonnevie-Ullrich will result in earlier and more frequent recognition of ovarian agenesis in the pediatric age group. This earlier recognition serves more than an academic interest since it should enable the physician to alert the parents to the probable future course of development of the child.

I wish to gratefully acknowledge the suggestions and advice given by Drs. L. H. Kyle and R. Hoefnagel in the preparation of this paper.

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ADDENDUM

What is believed to be a classical example of the syndrome has been recently observed in a newborn white female. The infant was the product of a completely normal pregnancy and delivery and weighed 6 pounds 3 ounces at birth. On initial physical examination, the following defects were noted: congenital webbing of the neck with prominent folding and redundancy of the skin of the nape of the neck, marked nonpitting edema of the dorsa of the hands, feet, and legs, and marked generalized cutis laxa. Also present were bilateral epicanthus, high-arched palate, and low implantation of hair on the nape of the neck. No skeletal anomalies were observed. The mother has had one previous stillborn infant, but there is no familial history of any other congenital anomaly.

REACTIONS FROM DPT IMMUNIZATION AND ITS RELATIONSHIP TO ALLERGIC CHILDREN

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THIS paper reports the results of a questionnaire concerning DPT (diphtheria, pertussis, tetanus) immunization and convulsions, and discusses this in relationship to allergy in children.

The problem of cerebral complications following the use of pertussis vaccine had been noted in isolated reports prior to the study of Byers and Moll.[1] These authors forcefully called this subject to the attention of the physician by collecting fifteen cases over a ten-year period at the Children's Hospital in Boston. They found about twice as many cases due to the disease itself in this same period. Toomey[2] considered the report of Byers and Moll so disturbing that he sought to obtain more data by sending a questionnaire to a number of pediatricians and writers on the subject of whooping cough. He asked, "Did the patients have a convulsion after vaccination?" There were thirty-eight cases. Data were available in twenty-five of these. Toomey stated that "twenty-three recovered completely, 2 died, 4 had subsequent convulsions, 4 were simultaneously ill with other diseases and 5 had convulsions previous to injections." One individual reported twelve with irreversible changes. Kong[3] collected eighty-two cases from the literature and reported two personal cases of cerebral complications following pertussis vaccination. Fifty-three of the eighty-two cases that Kong included were those of Byers and Moll and Toomey. In one of Kong's cases the paternal great-grandmother and the paternal aunt had asthma, a paternal uncle had eczema, the patient had eczema and an "asthmalike condition" during hay fever time. He received smallpox vaccination at 12 months and DPT at 15 months. At 26 months of age his sister developed whooping cough. Two weeks before this he had received BCG vaccination. It was thought desirable to protect him during the incubation of BCG, so he was given 40 billion pertussis organisms. Sixteen hours later he had a convulsion. He recovered completely except for abnormal electroencephalographic changes. Seven months later he had an unexplained convulsion from which he recovered in twenty-four hours. His subsequent physical and mental development were normal. On the basis of this single case, Kong stated that among the contraindications for pertussis vaccine were "allergoses of the child or the family (under no circumstances should vaccine be given in the acute phase of the special allergoses!)."

Kong's paper stimulated the editor of the *Letters* of The International Correspondence Society of Allergists[4] to poll the members of the society about their experiences with pertussis vaccine in allergic children. Some of

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the allergists had little experience with pertussis vaccine but they quoted their pediatric colleagues. There were thirty-five who were polled directly or indirectly. There were five convulsions reported with probably all patients making a complete recovery. One death was noted.

Recently the subject has been discussed by those interested in children with seizures. Melin[5] stated, "In my opinion the risk of a seizured child's contracting pertussis and eventually developing complications is more pronounced than the risk involved in the immunization procedure." Peterman,[6] Byers,[6] and Livingston[6] concurred with Melin. Lennox[6] was not in complete agreement with Melin. He felt that an existing lesion or an allergy to immunizing agents should carry a greater warning than a possible lowered threshold to convulsions.

Miller and Stanton[7] collected a number of cases dealing with the neurological sequelae of prophylactic inoculation. They described reactions from horse serum, typhoid-paratyphoid, diphtheria, pertussis, rabies, and tetanus inoculations. They observed one severe reaction from a Schick test.

It seemed apropos to restudy the problem because there was renewed interest in the relationship between pertussis vaccine, convulsions, and allergy in children. There appeared a definite need for additional data which would take into consideration that the vaccines had been refined considerably in the past few years. In addition to this, most people are giving the combined antigens, i.e., pertussis, diphtheria, and tetanus, in contrast to the older method of using a single antigen. Immunization is now started at a much younger age. With these facts in mind a questionnaire was sent to many of the men Toomey wrote, as well as to those working in the field, and to others in this country and Canada.

TABLE I. IN ANSWERING THIS QUESTIONNAIRE PLEASE REFER ONLY TO CHILDREN IMMUNIZED IN THE FIVE-YEAR PERIOD BETWEEN JAN. 1, 1949, THROUGH DEC. 31, 1953.

	Please underscore answer
1. Do you use DPT?	yes no
2. If YES—is it an alum, aluminum, or a fluid preparation?	alum aluminum fluid
3. At what age do you begin immunization?	1-2-3-4-5-6-7-8-9 months
4. Did any of your patients ever have a convulsion after vaccination?	yes no
5. If YES—did it occur after the	1st 2nd 3rd injection?
6. Was there fever associated with it?	yes no
7. Did it occur immediately after it?	12 24 36 48 72 96 (hours or longer)
8. Did the child completely recover?	yes no
9. If NO—was damage	mild moderate severe death?
10. Was there a past history of	allergy convulsions cerebral defect intercurrent illness?
11. Would you estimate the number of immunizations of DPT you have given in the past 5 years?	e.g.: 1,000 2,000 5,000 etc.

RESULTS

Table I shows the questionnaire. Fifty-six replied and their names are included at the end. All used the

TABLE II. KIND OF DPT VACCINE USED

	ALUM	ALUMINUM PHOSPHATE OR ALUMINUM HYDROXIDE	FLUID
No.	28	20	8

TABLE III. AGE IN MONTHS DPT IMMUNIZATION BEGUN

	1 MO.	2 MO.	3 MO.	4 MO.	5 MO.	6 MO.	7 MO.	8 MO.	9 MO.
No.	1	3	27	17	8	10	0	1	0

TABLE IV. DETAILED DESCRIPTION OF FIFTEEN CASES OF CONVULSIONS WITH ONE DEATH REPORTED BY NINE PEOPLE

AUTHOR	CASE NO.	KIND OF VACCINE	DOSE NO.	PAST HISTORY	FEVER ASSOCIATED	TIME ELAPSED BETWEEN INJECTION AND CONVULSION (HR.)	RECOVERED COMPLETELY	SEVERE DAMAGE	DEATHS
Blumenthal	1	$Al(OH)_3$	1	Negative	Yes	24-36	1		1
	2	$Al(OH)_3$	1	Negative	Yes	72-96			
Jorgenson	3	$Al(OH)_3$	2	Positive	No	10 min.	1		
Karelitz	4	$Al(OH)_3$	2	Positive	Yes	6	1		
Kohn	5	Alum	1	Negative	Yes	12	1		
	6	Alum	2	Negative	Yes	12	1		
Epstein	7	Alum	2	Negative	Yes	24-36	1		
	8	Alum	3	Negative	Yes	24-36	1		
Franklin	9	Alum	1	Negative	Yes	12	1		
Freeman	10	Alum	1	Negative	Yes	12	1		
Hartman	11	Alum	2	Negative	Yes	12	1		
	12	Alum	2	Negative	Yes	12	1		
	13	Alum	1	Negative	Yes	48		1	
Peterman	14	Alum	2	Negative	Yes	48		1	
	15	Alum	3	Negative	Yes	96		1	

TABLE V. COMPARISON OF REPLIES FROM TOOMEY'S QUESTIONNAIRE AND OUR OWN

	TOOMEY SERIES	PRESENT SERIES
No. replying	54	56
No. reporting convulsions	17	9
Convulsions	38	15
Complete recovery	24	11
Severe damage	12*	3†
Deaths	2	1

*Buchanan reported 12 cases presumably seen in consultation.
†Peterman reported 3 cases seen in consultation.

TABLE VI. DOSE IN WHICH SUBSEQUENT CONVULSION OCCURRED

	NO. 1	NO. 2	NO. 3
Byers and Moll	5	5	6
Toomey	6	4	2
Present series	6	7	

combined antigens, DPT. Table II gives the kind of vaccine used. It will be noted in Table III that there are more than fifty-six reporting. This is due to the fact that some reported beginning between 3 and 4 months or 5 and 6 months, etc. Table IV describes the patients who had convulsions. Dr. Peterman had no cases in his own practice but saw the three cases in consultation. It is interesting to note that all fifteen patients received the more slowly absorbed antigens. There was not a single case with a history of allergy. Only two children had any significant past history. One child had a cerebral injury with a history of convulsions; the other had recently recovered from influenza. In the last-mentioned case there was no fever with the convulsion.

Table V is presented to compare our results with those of Toomey. This seemed pertinent because Toomey's findings compiled in 1949 included material for some time prior to 1949. Those replying to the present questionnaire were asked to limit their findings to the five-year period between Jan. 1, 1949, and Dec. 31, 1953. Table VI notes the relationship between the dose and the convulsion in three different series of cases.

DISCUSSION

There were fifteen convulsions reported in the fifty-six completed questionnaires in our series. These occurred in the five-year period between Jan. 1, 1949, and Dec. 31, 1953. Toomey did not state the time interval but it was probably ten years or more. In his series both single and multiple antigens as either fluid or alum toxoid were used. For the most part there were a greater number of pertussis organisms given in each dose. Children were usually older when they received their immunization. Because of these variables in the two series, comparison is on somewhat tenuous grounds. Nevertheless, the number of replies to Toomey's questionnaire and our own were about the same with perhaps about the same number of immunizations. The replies would indicate that there was a decrease in the number of convulsions. There was approximately the same per cent of children who completely recovered. Incidentally, these findings were very similar to those obtained by the editor from a poll of thirty-five allergists.

All of the fifteen children who had convulsions received the more slowly absorbed multiple antigens. This was somewhat of a surprising finding because a review of the literature had led to the belief that the fluid toxoids were more likely to cause severe reactions. Sauer[8] stated, "Because the dose is smaller and absorption is delayed systemic reactions are less likely to occur and are seldom as severe with slow-absorbing antigens." Byers[9] stated that, "I do not think they [encephalopathies] are as common as they were when the saline suspension was used." However, Silverthorne[10] "does not consider alum precipitated vaccine better than fluid toxoid. For the most part in Canada we use DPT Connaught Laboratory fluid toxoid. This is less damaging, immunizes exceptionally well, and no relationship has been found in polio paralysis." In the older series such as Toomey's and Byers and Moll's, the vaccine was either the single or multiple antigen. Fluid and alum-precipitated toxoids were used. Byers and Moll and Toomey noted that there was no relationship between the first,

second, or third dose of pertussis vaccine and the occurrence of the convulsion. This was also observed in the present series.

Kong stated that allergy in the child or family was a contraindication to immunization. This statement appeared to have been made because an allergic child developed convulsions after receiving a booster dose of 1 c.c. that contained 40 billion pertussis organisms. This child had subsequent convulsions for unknown reasons with an abnormal electroencephalographic tracing. Not one child in our study who developed convulsions had any history of allergy.

Schick[11] said, "Allergy is not a contraindication to immunization." This is concurred in by such pediatric allergists as Clein,[12] Dees,[13] Fenton,[14] and Traisman.[15] On the contrary, allergy in a child is an even greater indication for immunization because it obviates the need for therapeutic animal sera. Peskin[16] found that tetanus toxoid could be given as safely to allergic children as nonallergic ones. Many agree that the danger of pertussis far outweighs that of vaccine inoculation even in children with seizures (Melin, Peterman, Livingston, Byers).

There are isolated statements in the literature that allergic children should be immunized differently. Thus Sauer says, "that allergic infants (especially those with generalized eczema) should not be injected until later." Crump[17] believes if the child is very allergic that one should skin test by the intracutaneous route. If there is any reaction, the antigens are given singly and intracutaneously. Miller[18] states that, "in asthmatic children fractional doses are advisable." Friedman[19] is of the same opinion and gives the injection intracutaneously. Doval[20] feels that the allergic child is more susceptible to local and general reactions although he thinks the improved vaccine in the past five years has resulted in less reactions. He uses smaller and more frequent doses in allergic children. In general, most pediatricians treat allergic children as they do nonallergic ones. Since primary immunization is now begun in most infants at 3 to 4 months, it would be difficult in most instances to determine if a child is allergic at that age. It would seem advisable in older nonimmunized allergic children and in allergic children requiring booster doses to use more caution. Volk[21] demonstrated that 0.2 c.c. of DPT will produce as satisfactory titers and less generalized reactions as 0.5 c.c. when used as a booster dose. Intracutaneous methods also produce high titers, so that the use of either smaller doses intramuscularly or intradermally should abolish any severe reactions.

The foregoing is not meant to imply that allergic reactions do not occur with pertussis immunization. Overall[22] had one case of angioneurotic edema with an anaphylactic reaction due to a booster injection. Arbeiter[23] stated that his "own daughter had a severe asthma attack and angio-neurotic edema one-half hour after a booster alum-precipitated pertussis v a c c i n e when she was nine years old. The dose used was the recommended dose of 0.5 c.c." He then went on to say that "I have had three children in my practice develop angio-neurotic edema and/or asthma within one hour after a booster dose or a dose other than the first one of the combined diphtheria, pertussis, tetanus alum-precipitated vaccine." Arbeiter knew of an infant who developed asthma following the

second and third injections of DPT. None of these children had a personal or family history of allergy. Painter[24] had a patient who developed an Arthus type reaction one week after the second injection in the opposite hip from the first injection. Both sites drained for more than one month and there was high fever for two weeks. Frazier[25] was called to see a patient in consultation who had received a DPT injection that was followed in a few hours by fever, coma, and death.

Faber and Miller[26] listed the following five categories that would include the principal possibilities to explain the convulsions following pertussis immunizations:

1. Constitutional peculiarities of the patients themselves.
2. Inadvertent intravenous injection of vaccine.
3. Antigen-antibody response to previous specific sensitization.
4. The presence of pyrogens in the bacterial bodies or in the water used in the preparation of the vaccine.
5. Damage to the cerebral vesse's from toxins of *Hemophilus pertussis*.

They considered Nos. 4 and 5 as the most likely possibilities although not ruling out any of the others. They felt that specific antigen-antibody reactions to pertussis antigen did not appear to adequately explain the convulsions. This has been the consensus of those writing on the subject, probably because reactions occur in children who have never been inoculated before and because the time relationships do not seem to follow the usual pattern observed from specific sensitization. Miller and Stanton studied the neurological sequelae following various types of vaccine immunization. It was their opinion that the basic mechanisms for the neurological complications were allergic although they admitted that the reactions after pertussis were different in that the illness was always cerebral.

One striking finding is the presence of fever in nearly every instance. It occurred in fourteen of the fifteen cases in the present series. Shaw[27] says that, "I believe convulsions and permanent damage especially occur in a previously brain damaged child; trigger mechanism." Silverthorne stated, "I do not believe that whooping cough vaccine or DPT has ever been a cause of convulsions in children in Canada or for that matter any place else if one is sure that they have eliminated all causes for convulsions. It seems very strange to me that if DPT or pertussis vaccine was a cause of convulsions, and convulsions not coincidental, that we should see them many more times when we know that hundreds of thousands of children are being continually inoculated with DPT." Adams,[28] as quoted by Friedman, believes that pertussis vaccine precipitates a convulsion by means of hyperpyrexia. At this time one might inquire if the convulsions could be on the basis of a simple febrile convulsion and the cerebral damage due, as Lennox stated, to an allergy to the immunizing agent, or to a previously pathological cerebral lesion.

In conclusion, it can be said that allergy was not found to be a contraindication to immunization, that the dangers of pertussis outweigh those of the disease itself, that allergic children are more in need of toxoid administration than nonallergic ones, and that the precautions and contraindications listed in the Report of the Committee on Immunization and Therapeutic Procedures for Infectious Diseases of the American Academy of Pediatrics may be applied to allergic children in

the first few years of life. It is probably safer to give older, highly allergic children, who either require primary immunization or a booster dose, small doses more frequently, administered intracutaneously or intramuscularly. The committee advocates that aspirin be given a few hours after the inoculation and then four hours later. Many allergists would readily condemn this procedure because they fear the development of aspirin sensitivity. However, if convulsions are on the basis of hyperpyrexia, aspirin may conceivably prevent convulsions. Aspirin is used so liberally and frequently by lay people and the medical profession that it seems dubious that the abolishment of its use following DPT immunization would make much difference in the total amount consumed.

SUMMARY

Fifty-six replies to a questionnaire noted fifteen convulsions following the administration of the more slowly absorbed multiple antigens, DPT, in the five-year period, 1949 through 1953. There were six convulsions with the first dose, seven with the second dose, two with the third dose. No child who had a convulsion had a history of allergy. There were eleven complete recoveries, three with irreversible brain damage, and one death.

The incidence of convulsions following DPT in the five-year period 1949 through 1953 apparently has decreased considerably.

Allergy is not a contraindication to immunization. The precautions, contraindications, and methods of immunization advocated by the Committee on Immunization of the American Academy of Pediatrics may be applied to allergic children in the first few years of life. However, it may be advisable in older highly allergic children who either require primary immunization or booster doses to administer smaller doses more frequently, either intramuscularly or intradermally.

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The Following Responded to the Questionnaires

1. Albrecht, Paul G.	Charlottesville, Va.	30. McCune, Donovan J.	Vallejo, Calif.
2. Andres, Ben	Longview, Texas.	31. McGee, W. Ambrose	West Palm Beach, Fla.
3. Bakwin, Harry	New York, N. Y.		
4. Bradford, W. L.	Rochester, N. Y.	32. Overall, James C.	Nashville, Tenn.
5. Byers, Randolph K.	Boston, Mass.	33. Peterman, M. G.	Milwaukee, Wis.
6. Clein, Norman W.	Seattle, Wash.	34. Pounders, Carroll	Oklahoma City, Okla.
7. Epstein, Joseph W.	Cleveland, Ohio.		
8. Felton, Harriet M.	Galveston, Texas.	35. Rambar, Alwin	Highland Park, Ill.
9. Fenton, Meryl M.	Detroit, Mich.	36. Rosenblum, Arthur	Chicago, Ill.
10. Flax, Leo Jay	Denver, Colo.	37. Ross, Sydney	Washington, D. C.
11. Franklin, John E.	New York, N. Y.	38. Sako, Wallace	New Orleans, La.
12. Freed, Alexander N.	Cleveland, Ohio.	39. Salmon, Geo. W.	Houston, Texas.
13. Freeman, Don Wm.	Denison, Texas.	40. Sauer, Louis W.	Evanston, Ill.
14. Gardner, Mariana	Denver, Colo.	41. Schick, Bela	New York, N. Y.
15. Goehle, Otto L.	Lakewood, Ohio.	42. Shaw, Edward B.	San Francisco, Calif.
16. Goldbloom, Alton	Montreal, Canada.		
17. Goodwin, T. Campbell	Cooperstown, N. Y.	43. Silber, Isadore B.	Cleveland, Ohio.
		44. Silverthorne, Leslie N.	Ontario, Canada.
18. Halpern, S. R.	Dallas, Texas.		
19. Hartman, Joyce I.	Shaker Hts., Ohio.	45. Snelling, Charles E.	Ontario, Canada.
20. Haymann, Walter	Cleveland, Ohio.	46. Strong, James C.	Dallas, Texas.
21. Hill, Lee Forrest	Des Moines, Iowa.	47. Thelander, Hulda	San Francisco, Calif.
22. Horesh, Arthur J.	Cleveland, Ohio.		
23. Jaquette, Jr., Wm. A.	Seattle, Wash.	48. Traisman, Alfred S.	Chicago, Ill.
		49. Traisman, Howard	Chicago, Ill.
24. Jorgensen, Gilbert M.	Los Angeles, Calif.	50. Weiner, Joseph	New Haven, Conn.
		51. Wier, Edward M.	Ft. Worth, Texas.
25. Kaliski, Sidney	San Antonio, Texas.	52. Yampolsky, Joseph	Atlanta, Ga.
26. Karelitz, Samuel	New York, N. Y.	53. Zohn, Benjamin	Brooklyn, N. Y.
27. Kohn, Jerome L.	New York, N. Y.	54. Wilkey, John R.	Seattle, Wash.
28. Lapin, Joseph H.	Brooklyn, N. Y.	55. Hamilton, Paul	San Marino, Calif.
29. Litchfield, Harry R.	New York, N. Y.	56. Volk, V. K.	Saginaw, Mich.

BREAST FEEDING: A FOUR-AND-ONE-HALF-YEAR EXPERIENCE

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INFANT feeding has become much safer and simpler than it was formerly, but there are still factors regarding the feeding of babies which require evaluation with a view to possible improvement. One such factor which deserves consideration is the apparent trend away from breast feeding. Formula-fed infants, in general, tend to do as well as breast-fed babies at the present time, but there are certain advantages of breast feeding which should be kept in mind.[1, 2] This study was undertaken to assay our results in infant feeding, and at the same time to ascertain our neonatal mortality and related data.

CLINICAL DATA

Our survey includes 3,937 infants born in St. Luke's Hospital, Fargo, from the beginning of 1949 through part of August, 1953. The number of infants, together with their birth weights and sex, may be seen in Table I. There are a comparatively large number of babies over 8 pounds at birth. This is probably accounted for by the predominantly Nordic racial background of people in this area, with a somewhat larger and heavier body build than exists in some parts of the country, although it is possible that a similar trend may be occurring on a nationwide scale. Males outnumber females to a slight extent, a relationship which has been found true in other such studies.[3] Among live births a ratio of approximately 1,065 males to 1,000 females exists generally as compared with a slightly higher ratio of 1,086:1,000 in our series. After wars, the proportion of male births tends to increase, probably due to the fact that mothers under 25 years of age have a higher percentage of male offspring than do mothers over that age.[3] The number of premature babies, 207, constituted 5.2 per cent of the live births; this is within the usual reported incidence of prematurity of 5 to 10 per cent of live births.[4]

After eliminating charts of some infants because of inadequate or uncertain data, there are 3,729 babies who have been studied from the standpoint of their feeding histories (Table II). Twenty-nine per cent of these infants, 1,104, were not put on the breast at all; 785 of the mothers in this group had no reason for not nursing their babies. Another 690 babies, 19 per cent of the total, were breast fed for less than two weeks. On the other extreme there were 658 infants, 18 per cent, who were breast fed for over six months, plus another 16 per cent who were breast fed for from two to six months. Another similar number, 18 per cent, were breast fed for from two weeks to two months. We did not differentiate between infants fed on

From St. Luke's Hospital and Fargo Clinic.

breast alone and those who received breast plus a supplementary formula. The majority of mothers who did not nurse their babies simply did not want to bother to breast feed, although some had tried with previous babies without success and did not care to attempt nursing again. Medical reasons for not nursing accounted for 14 per cent of cases in which breast feeding was not tried or was not carried through. There were a few cases in which a mother did not try because she said she was "too nervous." There were also a definite though small number who did not think that breast milk agreed with or satisfied their baby, and who found that formula feeding was more suitable.

for over two months, and 18 per cent of the total number nursed them for over six months. This might be considered with some satisfaction when compared with similar statistics from other parts of the country as reported by Bain[5] in 1948 from data gathered as part of a national survey of child health services made by the American Academy of Pediatrics and the United States Children's Bureau. For the United States as a whole, two-thirds of babies were on breast at the time of hospital discharge. The New England states and New York were lowest with 39 per cent, while the southern states were highest with 82 per cent; the central plains and mountain states were in between the two. These data

TABLE I. BIRTH WEIGHTS OF 3,937 INFANTS

FULL-TERM			PREMATURE		
POUNDS	MALE	FEMALE	POUNDS	MALE	FEMALE
Over 10	13	4	5 to 5½	46	60
8 to 10	565	312	4½ to 5	21	26
7½ to 8	377	312	4 to 4½	12	10
7 to 7½	388	375	3 to 4	14	11
6½ to 7	326	374	2 to 3	3	3
6 to 6½	193	276	Under 2		1
5½ to 6	92	123			
Total	1,954	1,776	Total	96	111
	3,730 (94.8%)			207 (5.2%)	

TABLE II. INCIDENCE OF BREAST FEEDING

	NUMBER	PER CENT
None	1,104	29
Less than 2 wk.	690	19
2 wk. to 2 mo.	674	18
2 to 6 mo.	603	16
6 mo. or longer	658	18
Total	3,729	100

DISCUSSION

There are several significant facts brought out by this survey of the feeding histories of over 3,700 infants. First of all, 71 per cent of mothers nursed their babies while in the hospital, 34 per cent nursed their babies

could not be carried beyond the hospital period, and Bain comments on the paucity of information regarding breast feeding in this country.

Bain included data previously reported in Great Britain, New Zealand, and Norway, showing the incidence of

breast feeding throughout the entire nursing period in those countries.[6] The incidence was considerably higher than that shown by our study. For example, the Ministry of Health of Great Britain reported 80 per cent of babies leaving the hospital on breast in 1946, 50 per cent on breast at 3 months of age, and 40 per cent still on breast at 6 months of age. A report from New Zealand in 1943 showed 89 per cent of infants on breast at 2 weeks, 71 per cent at 3 months, and 46 per cent at 6 months. Data reported from Oslo, Norway (1939 to 1944), showed 96 per cent of babies on breast at 2 weeks, 88 per cent at 3 months, and 82 per cent at 6 months. It seems possible that the high incidence of breast feeding in those countries at that particular time might possibly be partly accounted for by wartime economic factors, but this could not be entirely responsible for the high incidence reported.

In our study, 29 per cent of mothers did not nurse their babies at all. Of these, 273, or 7 per cent, of the total were primiparas. Another 14 per cent nursed for less than two weeks, indicating in some cases at least a half-hearted attempt to nurse or poor instruction in nursing technique. The most disturbing feature of all was the number of primiparous mothers who did not attempt to nurse their babies. A number of factors have a significant role in successful breast feeding[7] such as the health and breast structure of the mother, and the size, vigor, and health of the infant. However, it has been shown that the most important factor is a desire on the part of the mother to nurse her baby.[8] Efforts to convince the mother of the desirability of breast feeding must be made before the baby's birth to be effective; we have had extremely poor success in promoting breast feeding after the baby is born.

These findings were discussed with our associates in obstetrics as it was found that prenatal advice with regard to breast feeding was often lacking. It was found that efforts had been relaxed by the obstetricians because of overwork to some extent, but also from the feeling of at least one of them that we as pediatricians were not making sufficient efforts to keep babies on breast. In some instances in which the mother's milk decreased slightly during the first week or two, the first move of the pediatricians was to prescribe a formula and thereby tend to decrease whatever chances there were of the mother nursing the infant successfully.

There has also been a tendency on the part of some nurses to discourage mothers if their milk supply does not come in plentifully on the third or fourth day. This is a result of lack of knowledge and training, and is unavoidable at times. However, increased attention to nursing mothers and improved instruction to nurses are anticipated results of these findings.

It is probable that early discharge from the hospital on the fourth or fifth post-partum day has influenced breast feeding unfavorably. In an earlier study in this clinic,[8] 88 per cent of mothers were nursing their babies at the time they went home on the tenth post-partum day, either completely or in part. Those who had no visitors because of an encephalitis epidemic, and

thus had more rest, were found to have more milk and required less supplementation than an equal number who had daily visitors.

Management of breast feeding has been well outlined and described by Richardson,[2] and Barnes and his associates.[10] A flexible feeding schedule to allow the infant to nurse when hungry is helpful, especially in conjunction with rooming-in. We have had a limited rooming-in unit for the past year, and the results have been encouraging. Prenatal instruction for both parents, by both the obstetrician and pediatrician, has been found valuable in promoting satisfactory breast feeding,[10] and a better understanding of infant care in general. Care of the breasts and instruction concerning manual expression of milk are among the points of value. We are planning such classes at the present time.

There is difference of opinion as to whether a baby should nurse from one or both breasts at each feeding.[2, 10] Our practice has been to advise nursing at both breasts ordinarily, starting the feeding on alternate breasts, and limiting the total time to twenty or thirty minutes. Some infants prefer to nurse from only one breast at a feeding if the supply is large, and this arrangement is satisfactory in such cases. Until the milk comes in on the third or fourth day, it is customary to limit the time at each breast to from two to five minutes to avoid sore nipples. All are agreed that it is best to give babies only water during this time so that the breasts may be stimulated by more vigorous nursing than would be the case if the baby is appeased by a formula.

Further mention should be made of the finding that breast milk is not suitable for every baby. We have had a small but definite number of cases in which babies were much more comfortable on a formula than on breast, even though the supply of breast milk was adequate. This has occurred most often in cases in which the mother was unduly tense or excitable, although the reverse was occasionally true.

With the present knowledge of composition and sterilization of formulas, infants do as well generally on formulas as they do on breast. Exceptions to this may exist in the lower socioeconomic level, where proper sterilization of formulas may be lacking. In spite of the closer relationship of a nursing mother to her baby, a mother can have a warm, loving relationship to her infant by holding him for bottle feeding.[1] The likelihood of this close relationship is obviously greater if the infant is breast fed. There is no appreciable difference in the amount of colic in the two groups so far as we can determine. Formula-fed babies have firmer stools as a rule, and more often tend to be constipated. The incidence of regurgitation is about the same. Weight gain shows no appreciable difference; the majority of infants in both groups doubled their birth weight in 4 to 4½ months, and tripled their weight at 11 to 11½ months. As physicians, it would seem best to emphasize the advantages of breast feeding, but at the same time make it clear that all is not lost if breast feeding is unsuccessful.[1, 4] If too much stress is placed on breast feeding, we have seen mothers get a feeling of failure if unable to breast feed her baby.

SUMMARY AND CONCLUSIONS

1. Advantages of breast feeding are recognized. When breast feeding is not feasible, formula feedings are accompanied by equally favorable progress. Breast feeding should be encouraged in a reasonable way; this must be done prenatally to be effective.

2. The feeding histories of 3,729 infants born at St. Luke's Hospital show that 658 infants, 18 per cent, were breast fed for over six months. An additional 603 babies, 16 per cent, nursed at breast for from two to six months. This total of 34 per cent is considered adequate.

3. Eleven hundred four babies, 29 per cent, were not breast fed at all. Mothers of 785 infants had no reason for not nursing. Investigation showed that inadequate prenatal instruction was partly responsible; prenatal classes for parents are planned to remedy this fault.

4. Six hundred ninety infants, 19 per cent, were breast fed for less than two weeks. Six hundred seventy-four, 18 per cent, were breast fed for from two weeks to two months. It seems fair to say that those who were on breast for over two weeks were given a fair trial at breast, but that many who were weaned before that time failed to receive proper encouragement and instruction from pediatricians and nurses.

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CYSTINOSIS

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CYSTINOSIS is a disorder of protein metabolism characterized by the deposition of cystine crystals in various parts of the body, particularly in the reticuloendothelial system. It is seen mainly in children, but victims may survive to adolescence. While it is generally considered to be an extremely rare disease, Bickel and Harris[1] have recently estimated the incidence in the general population to be 1 in 40,000.

The literature on cystinosis has been extensively reviewed by McCune and associates[2] and recently by Bickel and co-workers,[3] while Freudenberg[4] and Rapoport[5] have contributed useful summaries. Of the fifty-four proved cases* of cystinosis reported up to 1952,[6] three were from the United States and the rest from Europe. Since 1952, five additional cases have been reported from the United States[7, 8, 9] and one from Britain.[10]

It seems likely that in the past some cases of cystinosis have been misdiagnosed as vitamin D deficiency rickets, resistant rickets, renal rickets, or renal dwarfism.[11] Since the correct diagnosis is easily made once the condition is suspected, a more widespread awareness of the special features presented may help to uncover further cases.

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*This figure does not include two cases, one reported by Maschas and associates[11] and the other by Streiff.[20] These have apparently escaped the notice of the reviewers.

CASE REPORT

First Hospital Admission.—G. M., an 11-month-old white male, was admitted to Children's Hospital, Winnipeg, on June 28, 1943. The entrance complaints were: constipation for three months, increased thirst, failing appetite, and failing development for two months. The patient was delivered at term, weighing 8 pounds 8 ounces. He was fed cow's milk and developed normally until 8 months of age, when the above complaints developed. He had received cod-liver oil and orange juice from the age of two months.

Family History: (See Fig. 1.) Both parents were alive and well. There was no history of kidney or heart disease, asthma or hay fever.

There were eight pregnancies. All newborn infants were healthy, well-developed, normal full-term babies, with a birth weight averaging 9 pounds. All but the last two were breast fed until 11 or 12 months of age.

1. Female, 22 years, alive and well.
2. Female, 21 years, alive and well.
3. Female, died at 14 months. Was taken to Winnipeg General Hospital because of poor appetite, polyuria, thirst, vomiting and retarded growth (noticed at 6 months). Died on day following admission from unknown cause.
4. Female, died at 3½ years. Similar symptoms. Terminal pneumonia.
5. Female, died at 18 months. Retarded development. Terminal diarrhea.
6. Female, died at 2½ years. Was in Children's Hospital at 19 months, weighing 13 pounds. Retarded development, thirst, marked polyuria. Diagnosed as rickets, acetonuria, and glycosuria on one occasion.

About ten days prior to death developed a sore mouth with loose teeth. (Scurvy suggested.)

7. Female, 9 years, alive and well.
8. Patient, 1 year. Only male child.

Physical Examination: On admission to the hospital, the patient weighed 18 pounds 4 ounces. His tissues were soft as from loss of weight. The costochondral junctions were prominent but no other clinical signs of rickets were present.

Laboratory studies during his eight-week stay in hospital showed the following: *X-ray* of the long bones (Fig. 2) suggesting rickets. *Urinalysis:* sugar, present in all specimens and ranging in concentration from 4.27 to 5.41 Gm. per twenty-four hours; acetone, always present; total organic acids, 7.4 to 10.8 meq. per kilogram of body weight per twenty-four hours, measured by the method of Van Slyke and Palmer (normal value, approximately 1 meq. per kilogram per twenty-four hours). *Blood chemistry:* fasting blood sugar, 80 Gm. per cent; a normal glucose tolerance curve; phosphorus, 1.2 mg. per cent; CO_2 combining power, 51 and 34 vol. per cent (two tests, six days apart); blood urea nitrogen, 15.5 mg. per cent.

The patient's temperature varied a great deal, ranging from 98 to 101.5° F. Diet for age was taken fairly well and appetite improved. Vitamin C and iron and ammonium citrate were given, and six weeks after admission the boy was put on a high phosphorus and low protein diet which was taken well.

The patient improved slowly and was discharged on Aug. 22, 1943, weighing 17 pounds 12 ounces. The diagnosis made was renal glycosuria and mild rickets. Ascorbic acid was to be continued at home.

Course: Following discharge he seemed much better for about three weeks. He gained weight, ate and slept well. He then developed a cold, became irritable, had a fever which lasted several weeks, and became very thirsty. He passed concentrated urine every hour and began to lose strength, finally being unable to get to his feet. On Oct. 21, 1943, he was brought to Children's Hospital for treatment of a papular rash over the back, abdomen, and limbs. His weight at this time was 19 pounds 8 ounces. Two months later (at age 17 months), his weight was unchanged, although his appetite was satisfactory, and his thirst had diminished. He now had a fondness for sour foods. Clinical and x-ray signs were similar to those on first examination.

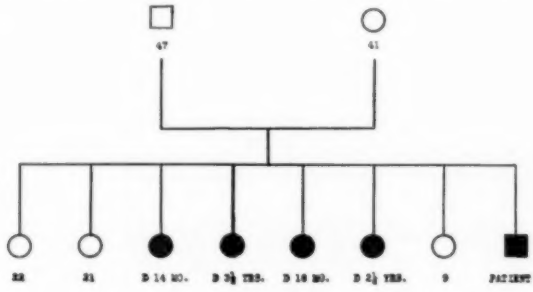

Fig. 1.—Family pedigree (see text).

On re-examination on April 4, 1944, the patient no longer took sour foods but enjoyed meat, eggs, and potatoes. He was now able to climb stairs and to stand if holding on to some support. He weighed 20 pounds 1 ounce and looked better, but his wrists were larger and the costochondral junctions were more palpable. X-ray of

the long bones showed quite marked changes, indicating rickets. Potassium citrate, citric acid, and ascorbic acid were prescribed.

During the next two years, the patient did not grow normally, but he was mentally alert. Although he had started to walk at the age of 2, he was too weak to keep it up, and even at the age of 4 preferred to crawl. Concentrated vitamin D drops were given for more than a year before his second hospital admission.

Fig. 2.—Patient, July, 1943.

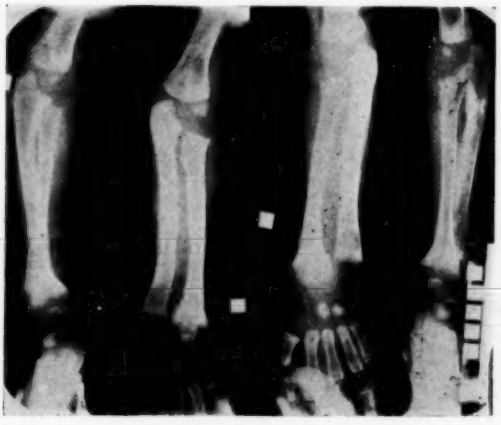

Fig. 3.—Patient, August, 1946.

Second Admission.—On Aug. 9, 1946, the patient was readmitted with a complaint of "stiff hands and stiff feet." He now weighed 20 pounds. X-ray of the long bones revealed marked changes indicating active rickets present over a long period (Fig. 3).

Laboratory examination revealed the following: *Urinalysis:* daily albumin excretion of 40 to 500 mg. per twenty-four hours; negative tests for sugar, acetone and diacetic; Mosenthal test, specific gravity 1.003 to 1.010. *Blood chemistry:* blood urea nitrogen, 24.08 mg. per cent.

The tetany with respect to carpapedal spasm was controlled with 10 ml. of 10 per cent calcium gluconate given intravenously. The blood calcium level, measured next day, was 7.2 mg. per cent. Calcium chloride (1.3 Gm.) was administered every four hours for three days; subsequently calcium gluconate was given instead of the chloride.

The patient was discharged on Aug. 22, 1946, with his appetite much improved and weighing 22½ pounds. Calcium gluconate tablets (1.3 Gm., t.i.d.) and cod-liver oil* were continued at home.

Course: During the next four years the child progressed fairly well. He was usually a very happy child, never cried and played well with other children. He learned to read and write although he did not attend school. His gait, while still wobbly, had definitely improved. He ate well, but was usually constipated and had to be given milk of magnesia regularly. In February, 1950, however, the patient twice suffered a painful recurrence of spasm of the extremities which was relieved by intravenous administration of 0.16 Gm. of calcium gluconate.

*Mead Johnson, Oleum Percomorph; 1.2 ml. daily, containing 26,600 vitamin A units and 3,700 vitamin D units.

Third Admission.—The patient was readmitted on Feb. 24, 1950, at the age of 7½ years, for investigation in the light of recent literature on cystinosis. Physical examination revealed: weight, 29½ pounds; obvious dwarfing (Fig. 4); misty corneas; some photophobia; protuberant abdomen but no masses; seborrhea of skin and ichthyosis; marked deformities in the legs; no rickety rosary. Chvostek's and Trousseau's signs could not be elicited. Blood pressure was 102/60.

Fig. 4.—Patient, February, 1950, aged 7½ years.

Laboratory tests gave the following results:

Blood:	Calcium	6.23 mg. %
	Phosphorus	2.86 mg. %
	B.U.N.	47 mg. %
	CO_2 C.P.	50 vol. %
	Fasting sugar	91 mg. %
	Vitamin A	161 gamma %
	Carotene	440 gamma %
	Alkaline phosphatase	34 K.A. units
	Serum proteins	6.81 Gm. %
	Albumin	4.14 Gm. %
	Globulin	2.67 Gm. %
	Thymol turbidity	½ unit
	Thymol flocculation	negative
	Cephalin cholesterol flocculation test	negative
Urine:	Specific gravity	1.008
	Albumin	180 mg./24 hr.
	Sugar	none
	Acetone	none
	Ammonia	110 mg./24 hr.
	Calcium	45 mg./24 hr.
	Phosphorus	656 mg./24 hr.
	Cystine crystals	none
	Phenolsulfonthalein test	1 hr.: 4.7% excretion 2 hr.: 5.3% excretion

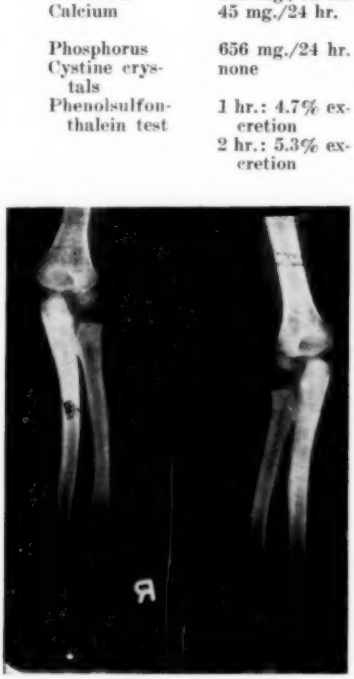

Fig. 5.—Patient, February, 1950.

Comprehensive x-ray examination gave the impression of chronic rickets which had produced rather marked deformities. It is clear, however, from Fig. 5 that the activity was not as marked as it had been three and one-half years earlier.

On the basis of the clinical findings, cystinosis was suspected. The bone marrow was therefore examined for cystine crystals, but none were found. Slit-lamp examination of the eyes, however, showed that the corneas were packed with crystals.

Since defective excretion by the kidney had been suggested as the

cause of cystine deposits in various sites (see discussion), an attempt was made to examine more fully the capacity of the kidney, particularly with regard to its ability to excrete amino acids. Paper chromatography was utilized* in the detection and semi-quantitative estimation of amino acids in the patient's urine prior to and following the intravenous administration of 490 ml. of Aminosol.† The results are listed in Table I. It is of interest that no evidence for any sulfur-containing amino acids was obtained in fasting urine, but that when presented with an overload was not completed successfully. It was ascertained, however, that the fasting level of blood amino acids was approximately double the normal value.

Following discharge, the patient was seen in the outpatient department several times, usually because of attacks of tetany. Some results of routine tests on these occasions are included in Table II, which summarizes the main features of the patient's blood chemistry.

For about a year (September, 1950, to October, 1951) the patient appeared much improved. He had no

TABLE I. PAPER CHROMATOGRAPHY OF URINARY AMINO ACIDS

Fasting Urine	Amino acids found: Glutamic acid Aspartic acid Glycine Alanine Leucines	*Note:* No evidence for sulfur-containing amino acids was found.		
Following I.V. Aminosol	Amino acids found at various time intervals after administration:			
1st Hour	*2nd Hour*	*3rd Hour*	*4th Hour*	*5th-7th Hour*
Same as fasting	Same as fasting + Lysine Threonine Histidine Proline Hydroxyproline Cystine	Same as 2nd hour + Methionine Tyrosine Tryptophan	Uniform increase in all components	Aspartic acid Glutamic acid Alanine Cystine Leucines Valine Proline Tryptophan Tyrosine

of all normal-occurring amino acids in the blood, the kidney was able to excrete all of them, including the relatively insoluble cystine. It, therefore, appeared that the deposits of crystals in the eyes, if consisting of cystine, were not likely due to inefficient excretion by the kidney.

The patient was discharged on March 22, 1950, with instruction to take Drisdol daily (10,000 units).

Fourth Admission.—On April 27, 1950, the patient was readmitted for the purpose of doing an amino acid tolerance test. Unfortunately, this spells of tetany and was out every day. The father was anxious for the boy to start school. There was still a marked rachitic deformity, but the boy was happy. The blood urea nitrogen and serum phosphorus levels were rising while serum calcium was still low (see Table II).

In September, 1951, the patient was given eight (500 mg.) methionine tablets daily for a week, the object being to see if he would excrete "extra" cystine in the urine. The results were negative (see discussion).

During a two-week period in October, 1951, the patient developed frequent attacks of tetany, particularly in the afternoon. He became tired and listless and at times suf-

*We are indebted to Mr. I. W. Coleman of the St. Boniface Hospital, Winnipeg, for the chromatographic analyses. A modification of the method of Consden and associates[12] was used.

†Abbott's A4421 protein hydrolysate with dextrose.

fered from severe photophobia. He was no longer subject to polydipsia and polyuria, but his breathing was labored.

On Nov. 5, 1951, he looked pale. His breath was uremic, and there was some puffiness of the upper eyelids. Blood pressure was 120/80.

Fifth Admission.—On Nov. 5, 1951, the patient was readmitted for investigation. Physical examination revealed a pale skin, no rash, protuberant abdomen, small umbilical hernia, and marked bilateral anterior bowing of the tibia.

Laboratory tests during the week November 5 to 10 gave the following results: *Blood:* Ca, 3.62 to 4.45 mg. per cent; P, 10.1 mg. per cent; blood urea nitrogen, 119 mg. per cent; CO_2 combining power, 23 vol. per cent; pH, 7.23; hemoglobin, 4.2 to 6.5 Gm. per cent; red blood count 2.17 M; packed cell volume, 15.5; mean corpuscular volume, 71 $c\mu$; mean corpuscular hemoglobin concentration, 27. *Urine:* Specific gravity, 1.010; pH, 6.0; albumin, 250 to 300 mg. per cent; ketone bodies, none; leukocytes, 2 to 10; red blood cells, 3 to 6; epithelial cells, a few; some debris, but no cystine crystals.

X-rays showed additional healing of rickets since February, 1950.

Treatment given was intravenous calcium gluconate (500 mg.), 500 c.c. packed cells, and 250 c.c. whole blood. The patient was then discharged. Provisional diagnosis: Fanconi syndrome, renal rickets, and uremia. He was continued on Drisdol, 10,000 units daily, and soluble calcium (Sandoz), 1 teaspoon, t.i.d.

When seen in the outpatient department on November 23, the patient seemed much better. He had more pep, had been out every day, no attacks of tetany, more frequent loose stools. A flat plate of the abdomen showed no abnormal calcification. Kidney shadows were probably visible, and if so, were quite small.

Sixth Admission.—The patient was readmitted on Dec. 17, 1951, for transfusion. He had experienced loss of appetite, listlessness, and weakness for the preceding two weeks.

Physical examination revealed a 9½-year-old boy weighing 33½ pounds and standing 37 inches tall. The liver was palpable 3 inches below the costal margin. Pulse was 80. Blood pressure was 140/100.

Blood examination: Hemoglobin was 7.5 Gm. per cent; Ca, 5.0 mg. per cent; P, 14.3 mg. per cent; blood urea nitrogen, 205 mg. per cent. *Urine:* Specific gravity, 1.012; albumin, 300 Gm. per cent; white blood count, 1 to 4 per high-power field.

The patient was transfused up to 11.1 Gm. of hemoglobin and then discharged. He died at home on Jan. 1, 1952.

TABLE II. SUMMARY OF PATIENT'S BLOOD CHEMISTRY

DATE	P MG./100 ML.	Ca MG./100 ML.	B.U.N. MG./100 ML.	CO_2 COMBINING POWER VOL. %	ALK. PHOSPHATASE K.A. UNITS	pH
June 28, 1943	1.2	–	15.5	51 & 34	–	–
Aug. 9, 1946	2.0	7.2	24	–	–	–
Feb. 24, 1950	2.8	6.2	47	50	34	–
Mar. 21, 1950	2.9	7.2	29	–	31	–
Mar. 26, 1950	2.9	6.0	–	–	–	–
Apr. 24, 1950	–	7.2	–	–	–	–
Apr. 27, 1950	2.7	7.1	–	–	–	–
July 24, 1950	2.0	6.4	41	–	35	–
Sept. 25, 1950	–	5.6	43	–	14	–
Nov. 13, 1950	3.2	5.9	–	–	–	–
Apr. 10, 1951	5.0	7.3	74	–	–	–
Nov. 6, 1951	10.1	3.6	119	23	–	7.23
Dec. 17, 1951	14.3	5.0	205	–	–	–

Post-mortem Examination.—The autopsy was performed by Drs. J. Hoogstraten and C. Sorenson about twenty-seven hours post mortem. Examination permission was restricted to the thorax and abdomen.

Dr. Hoogstraten has kindly allowed us to publish his report and to reproduce one of his photographs. The pertinent macro and micro findings are abstracted from Dr. Hoogstraten's report.

Neck. Larynx and Trachea: There is considerable edema and inflammation of the epiglottis and glottis and a small amount of sticky mucoid exudate adheres to the mucous membrane. There is a slight inflammation of the mucous membrane of the trachea; the trachea and bronchi are patent.

Parathyroids: The four parathyroids together weigh 45.5 mg. Their measurements are as follows: 0.4 by 0.3 by 0.15 cm.; 0.4 by 0.2 by 0.20 cm.; 0.4 by 0.3 by 0.1 cm.; 0.3 by 0.2 by 0.1 cm.

Thorax: The subcutaneous tissues are noticeably edematous and the muscles of the thoracic wall are paler than normal, moderately soft and edematous. *Pericardium:* the visceral and parietal layers are pale, smooth, and glistening and there are a few cubic centimeters of pale straw fluid. *Heart:* the heart (150 grams) is larger than normal; all the chambers are dilated, and their walls somewhat hypertrophied. The papillary muscles are very prominent. Starting just above the aortic valve and extending to the bifurcation of the aorta are scattered irregular, yellowish, soft subintimal plaques. They appear to be especially prominent around the ostia of the celiac and superior mesenteric arteries. They vary in size from 2 mm. to slightly more than a centimeter. They are most prominent in the ascending aorta.

Abdomen: Liver weighs 554 grams. The capsule is thin and transparent. The cut surface of the liver is light brown in color, with minute, pale yellow flecks scattered heavily over all the cut sections of the liver. These flecks are of a size which just allows distinction with the naked eye. Lobular markings are visible, but are not distinct. The intra- and extrahepatic branches of the portal vein and bile ducts are normal. *Spleen* weighs 55 grams. The capsule is thin and transparent. The cut surface is red-brown in color; superimposed on this background are numerous and prominent pale yellow striae, which, on closer inspection, appear as branching filaments. The malpighian bodies appear distinct from these as gray translucent pin-point areas. The "red" pulp of the spleen has a more brownish than red color. *Kidneys:* The left weighs 15 grams and the right 18 grams. They measure 5.4 by 0.3 by 1.5 cm. The capsule strips with a slight difficulty and is associated with a small amount of decortication. The surface of the kidney has a finely granular appearance, with scattered yellow flecks occasionally visible. The cortical and medullary markings are indistinct and both appear thinned, the cortex measuring 0.1 mm. in thickness and the medulla 0.4 cm. The pelvis is not dilated, and the wall of the pelvis appears thickened, but the mucous membrane is pale, smooth, and glistening.

Gastrointestinal Tract: There are no malformations and the serosal surface is pale and glistening. The stomach contains some brownish-colored fluid; the underlying mucosa is not remarkable. Starting at terminal duodenum, most marked in jejunum, but also seen to a lesser extent in ileum, are seen numerous pale yellow flecks. These are seeded in varying density throughout jejunum, while in ileum they are confined to the summits of the folds. None are visible in large bowel.

Bones: The sternum presents a striking abnormality and consists almost entirely of cartilage containing five small centers of ossification measuring up to 0.9 cm. in diameter. Its

structure resembles that of a newborn child. The ribs appear grossly normal and there is no abnormal enlargement of the costochondral junction. The line of provisional calcification is slightly irregular, but not thick or yellowish and opaque. The marrow is pale red.

Frozen sections of liver revealed large deposits of crystals. An ammoniacal extract of liver tissue exhibited an abundance of irregularly hexagonal crystals, apparently cystine (Fig. 6).

Histological Findings: Parathyroids: The four parathyroids exhibit a uniform histology, and consist of closely packed cells with relatively abundant clear cytoplasm and small round or oval nuclei with closely packed, finely punctate chromatin. Small capillaries traverse the glands. No abnormal cytology or histology within these glands can be detected, but they are undoubtedly larger than normal.

Thymus: The thymus is atrophic. Hassel's corpuscles are largely cystic and filled with eosinophilic debris. Surrounding the corpuscles are groups of reticular cells with irregularly oval, somewhat hyperchromatic nuclei. The remaining stroma of the gland consists largely of fibrous tissue containing relatively small numbers of lymphocytes, but scattered throughout are not infrequent macrophages or histiocytes, whose cytoplasm contains small refractile crystals. These are still apparent in paraffin sections and are doubly refractile in polarized light.

Heart: The myocardial fibers stain reasonably well. Some of the fibers have unusually large nuclei, indicating some degree of hypertrophy. There is no increase in interstitial fibrous tissue and no inflammatory infiltrate except for a small but very definite focus of polymorph infiltration in the interstitial connective tissue of the myocardium of the aortic valve ring. There is a noticeable fibroblastic proliferation beneath the intima of the aorta, which is focal in distribution. The deeper portions of the subintimal fibrosis contain vacuolated areas, but no macrophages or lipophages are seen.

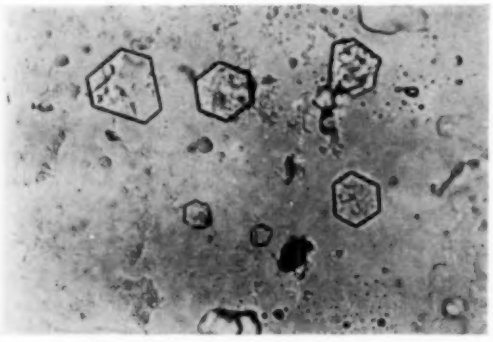

Fig. 6.—Cystine crystals from ammoniacal extract of liver tissue.

Liver: The sinusoids are dilated and the columns of parenchymal cells are somewhat narrowed. The von Kupffer cells contain many small refractile, clear, colorless crystals of nondescript shape which appear doubly refractile when viewed with a piece of polaroid below the condenser and above one ocular. The cytoplasm of the Kupffer cells is distended with the small crystals. No crystals are seen within the parenchymal cells or in the connective tissue of the portal

tracts. There is no increase in connective tissue within the portal tract and there is no inflammatory infiltrate.

Spleen: The spleen shows essentially normal architecture. There are innumerable macrophages with small pyknotic nuclei and whose cytoplasm is packed with somewhat refractile crystals of nondescript shape. The crystals are almost colorless and clear, but where seen in greatest aggregations, they appear to have a slightly yellowish color. These macrophages are aggregated mainly within the fibrous trabeculae and in the connective tissue surrounding the arterioles. None appear to lie within the sinusoids. These crystals, as in the other situations, are doubly refractile when viewed in polarized light. Small islands of hemopoietic cells are present within the sinusoids. There is a noticeable degree of hyaline thickening of the arteriolar walls.

Lymph Nodes: Occasional macrophages containing crystals are seen within the lymph nodes. The nodes otherwise exhibit normal histology and cytology.

Kidneys: The kidneys show a remarkable degree of parenchymal atrophy. No normal glomeruli can be found. The vast majority of glomeruli are completely hyalinized. The hyalinization appears to have progressed from the glomerular capillary tufts, and there is little or no evidence that the hyalinization has progressed from a thickening of the parietal layer of Bowman's capsule. In periodic acid-Schiff preparations, the hyalinized glomeruli are deeply fuchinophilic. Those few glomeruli which are not completely hyalinized show thickening of the capillary walls. The arterioles within the atrophic parenchyma cannot be identified with certainty. The tubules exhibit extreme degrees of atrophy, their lumens are dilated, and the epithelium is low and cuboidal. The basement membrane of many of the tubules is thickened. The lumen of the tubules of the lowermost portion of the nephron is filled with amorphous eosinophilic material. There is a relative increase in interstitial connective tissue, and the interlobar, arcuate, and interlobular arteries appear tortuous and relatively prominent because of the atrophy of the surrounding parenchyma. Arteriosclerotic changes are present within the pelvic branches of the renal arteries. The interstitial connective tissue is infiltrated with moderate numbers of lymphocytes. Nowhere are crystals seen within the kidney tissue.

Intestine: Sections show essentially normal histology. There is a moderate degree of autolysis of the superficial layers of the mucosa. Nowhere is there evidence of deposition of crystals.

Pancreas: The pancreas exhibits normal histology and cytology. The islets appear normal in hematoxylin and eosin preparations; there is no increase in interstitial connective tissue, no inflammatory infiltrate, and no deposition of crystals.

Bone: Sections examined are from sternum and costochondral junction. Section of sternum shows apparent normal enchondral ossification. No microscopic abnormality can be detected, although the gross appearance of the sternum is strikingly abnormal. Section through the costochondral junction shows small rounded islands of hyaline material lying between the bony trabeculae. The material resembles the matrix of hyaline cartilage, but is devoid of cartilage cells, except in one area. There is a slight increase in delicate connective tissue (fibrous) between the trabeculae immediately adjacent to the costal cartilage. There is no abnormal vascularization of the cartilage, and the cartilage cells themselves are arranged in fairly regular parallel columns. The bone marrow in both situations is of approximately normal cellularity, and exhibits per-

haps a moderate erythropoietic hyperplasia. In neither section of marrow can crystals be detected.

Comment: The renal lesion is the major pathological feature in this child, and the child succumbed because of renal failure. The pathogenesis of this important lesion, however, is not understood. The essential lesion appears to be glomerulosclerosis, but its pathogenesis is not known. There is nothing to suggest chronic glomerulonephritis, from the standpoint that there is no capsular proliferation and no hyalinization progressing from the parietal layer of Bowman's capsule. The lesion appears to be a slow and progressive hyalinization of the capillary tufts similar to the lesion of arteriolar nephrosclerosis with, of course, subsequent atrophy of the renal tubules. Unlike arteriolar nephrosclerosis, however, it is impossible to identify with any certainty any remaining arterioles in these kidney sections.

Although there is a noticeable lymphocytic infiltrate in the interstitial tissue, the lesion is not believed to represent chronic pyelonephritis subsequent to cystinuria. There is no inflammatory infiltrate in the pelvic mucosa.

Final Anatomic Diagnosis: (1) Cystinosis, with deposition of cystine crystals in macrophages within liver, spleen, lymph nodes, thymus. (2) Renal glomerular sclerosis and tubular atrophy. (3) Parathyroid hyperplasia. (4) Rickets (renal) and dwarfism. (5) Myocardial hypertrophy. (6) Arteriosclerosis. (7) Pulmonary hyperemia and edema. (8) Subcutaneous edema.

Chemical Isolation of Cystine From Tissues: A quantitative analysis of cystine in the liver, spleen, and heart was performed in the following manner. Fresh frozen samples of these organs were macerated in a cold room by means of six hack-saw blades which were strapped together to form a wide cutting surface. The weighed "sawdust" of each sample was then thoroughly ground by means of a mortar and pestle with a volume of 10 per cent trichloroacetic acid approximately equal to one-half the weight of tissue taken and washed into a centrifuge tube with a further small quantity of trichloroacetic acid. The total volume of trichloroacetic acid used for each sample was equal to the weight of tissue taken. After centrifuging, the samples were treated further according to the method described by King and Lochridge.[13] The yields of twice recrystallized material on a wet tissue weight basis were: liver, 0.7 per cent; spleen 2.2 per cent; heart, 0.0 per cent.

That the crystalline material was indeed cystine was shown by the characteristic hexagonal shape of the crystals under the microscope, by tests for labile sulfur, and by the formation of characteristic crystals of cystine phosphotungstate as described by King and Lochridge.

DISCUSSION

Before the recent publications of Bickel and associates,[3] a great deal of confusion reigned over complex syndromes which were variously labeled Lignac's disease, Fanconi syndrome of childhood, de Toni-Debre or Fanconi-de Toni-Debre syndrome. It now appears that these are all one and the same disease which may occur in either acute or subacute form, or in chronic form. The case described belongs to the latter category.

In the chronic form of cystinosis, or Lignac-Fanconi disease to use Bickel's new designation, the three most striking clinical features are dwarfing, bone changes which include osteoporosis, rickets and deformities, and photophobia. The most constant finding is dwarfism, but bone changes and photophobia are common. Tetany is not uncommon and would occur more frequently but for acidosis

which is usually present. Nonspecific findings include pyrexia, constipation, vomiting, polydipsia and polyuria, refusal of solid foods, dehydration, and state of profound collapse which may end in sudden death.

Laboratory findings in chronic cystinosis vary considerably from case to case.[3] There may be an early glycosuria which diminishes or stops altogether in later stages. Ketonuria is rarely found but albuminuria is common. A general aminoaciduria, which is striking in the acute form, is less remarkable in the chronic form and on occasion may be completely absent, hence easily overlooked. There is an increase in organic acids in the urine which may vary from just above normal to as much as ten times normal values. Blood changes include acidosis which may vary considerably in severity. Occasionally, even normal CO_2 values are obtained. Serum calcium levels may be normal or diminished, while phosphorus values are usually low, except in the terminal stage of the disease. Hypopotassemia has recently been noted and is believed to play an important role in the disease. In the later stages, there is an increasing retention of nitrogen and kidney insufficiency. Certain of these findings are illustrated by Table II, which summarizes some of the blood chemistry of the case reported in this paper. Of particular interest is the final value of the serum phosphorus (14.3 Gm. per cent); this is higher than any previously reported in the literature on cystinosis.[14]

Cystinosis is reported to have occurred in siblings[1, 15, 16] but there is no record of its occurrence in different generations of the same family. Our case appears to be an example in point. Four sisters died at an early age of symptoms similar to that of the patient, and it seems probable, in retrospect, that they suffered from the same disease.

Various theories have been proposed regarding the fundamental defect in cystinosis. The basic problem, stated simply, is whether cystine storage is due to impaired kidney excretion, or to some prerenal defect in protein metabolism. Baar and Bickel[6] have examined these theories critically, and conclude that in the light of recent discoveries, a faulty renal mechanism cannot be sustained as the primary cause of the disease. Their own thesis is that cystinosis is due to a general disturbance in amino acid metabolism, probably in its anabolic phase.

While Baar and Bickel have not been able to explain all the findings in cystinosis, their theory does account for its main features. Thus, a defective intracellular utilization of amino acids in protein synthesis leads to an aminoacidemia, and, hence, aminoaciduria. Cystine, being the most insoluble of the amino acids in cellular fluids, tends to precipitate in the sites of most active protein synthesis, namely, the reticuloendothelial system; hence, cystinosis is but the visible manifestation of a general defect in protein metabolism. A diminished production of protein, furthermore, results in dwarfism and possibly in some of the bone changes which are seen. Kidney damage, they suggest, may be due to the excessive excretion of organic acids, the origin of which is thought to lie in disturbed transamination. Partial loss of the

kidney's function in maintaining isoionia of the plasma leads to hypopotassemia, acidosis, and dehydration.[14] The terminal hyperphosphatemia likewise results from advanced kidney destruction. Rickets is explained by faulty absorption of calcium and phosphorus from the intestine.[11] Glycosuria, where it exists, is probably due to glycose formation from amino acids by the kidney.[11]

According to an earlier theory advocated by Freudenberg, the metabolic defect in cystinosis was identical with that in cystinuria. The normal metabolic pathway for methionine involved changes through homocysteine to cystathionine to cysteine followed by oxidation to sulfate, but for the two diseases mentioned he postulated a failure in the last step, resulting in increased oxidation of cysteine to cystine rather than to sulfate. It was with this theory in mind that our experiment, the administration of methionine to the patient, was performed (see fourth admission). According to well-known results with cystinuries, "extra" cystine is excreted. Our results were negative, and at that time were interpreted as not supporting the diagnosis of cystinosis which was suggested by earlier slit-lamp microscopy. While we cannot support this theory now it should, perhaps, be pointed out that an experiment by Maschas and coworkers[17] yielded results which could be interpreted in favor of the theory. In a paper which has gone unnoticed in literature on cystinosis, these authors report cystinosis on the basis of ocular findings in an Egyptian who was 19 years of age at the time of diagnosis. This young man had suffered painful lumbar attacks and had excreted a large number of cystine calculi during the previous eighteen months. Proceeding on the assumption that the metabolic defect lay in the failure of cysteine to be oxidized to sulfate, Maschas administered methylene blue intravenously to assist the enzymic systems in the oxidation process. The methylene blue seemed to have the desired effect since the urinary organic sulfur–total sulfur quotient fell to a more normal level. The patient thereafter received regular injections, and suffered no recurrence of lumbar crises although several further calculi were passed in the urine. This case is certainly an unusual one and merits further study.

Freudenberg held, moreover, that cystine storage was due to inefficient excretion of excessive amounts of cystine by infants and young children with their "functionally immature kidneys." Paper chromatography of the urinary amino acids excreted by our patient prior to and following the intravenous administration of Aminosol (see third admission and Table I) revealed that he had no difficulty in excreting cystine or any other amino acid when presented with an overload in the blood. Again a diagnosis of cystinosis base on Freudenberg's hypothesis was contradicted by experimental results. It is now known that, contrary to Freudenberg, cystinuria is possible in infants and young children.[18]

The clinical picture presented by cystinosis may be indistinguishable from that of resistant rickets, renal rickets, renal acidosis, celiac disease, or even of galactosemia and glycogen disease. Chemical findings are too

variable to be of diagnostic value but may be used as confirmatory evidence. The pattern of the aminoaciduria, for example, when it is present, is sufficiently characteristic of cystinosis[11] to distinguish this condition from another in which an aminoaciduria may also be present. Final proof of cystinosis, however, rests on the demonstration of cystine storage. This is accomplished in vivo most readily by a lymph node biopsy,[11] although slit-lamp microscopy is satisfactory where the investigator is experienced and the child is cooperative. Examination of the bone marrow for crystals may be disappointing[19] and a negative result after hours of search, as in our case, does not exclude cystine storage.

The prognosis in cystinosis has generally been considered hopeless. No case of survival beyond the age of 16 years is known, unless the case of Maschas and associates be accepted as an exception. Recently Bickel and co-workers[11] have given a preliminary account of encouraging results following therapy directed against rickets, acidosis, and hypopotassemia. The most surprising and perhaps most important effect of prolonged alkalinization was the gradual reduction and eventual disappearance of aminoaciduria and glycosuria.

In view of the fact that studies of the so-called "inborn errors of metabolism" have contributed to a knowledge of normal metabolic pathways, then it is conceivable that cystinosis might prove similarly useful in studying protein synthesis in vivo. The template theory of protein synthesis[21] might form the basis of future experiments in elucidating the mechanism of the disease and thereby indicate the way to a rational therapy. Perhaps a primary template is damaged or perhaps there is some defect in the enzyme system which prevents amino acids from being utilized. Here, again, a study of the abnormal might lead to a knowledge of the normal.

SUMMARY

This paper reports a case of cystinosis in a 9-year-old boy. The diagnosis was definitely established following post-mortem examination, although previous slit-lamp examination of the eyes had revealed crystalline deposits suggestive of cystinosis.

A number of investigations were performed, including the feeding of methionine to the patient, the chromatographic analyses of urinary amino acids, and the post-mortem isolation and quantitative determination of cystine from heart, liver, and spleen.

A brief review on the clinical features, laboratory findings, pathogenesis, diagnosis, and treatment of the disease is presented in the discussion.

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INTUSSUSCEPTION IN THE NEWBORN INFANT

With Spontaneous Expulsion of the Intussusceptum; A Case Report and Review of the Literature

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INTUSSUSCEPTION of the intestinal tract is not an infrequent condition encountered in infancy and childhood. It is found most frequently in males during the ages 6 to 18 months. During the newborn period, however, this disease is quite rare (Table I). In a review of large series in the literature, we have been able to find an incidence of only 0.3 per cent of cases occurring during the first month of life in a total of 5,966 cases of intussusception. In as exhaustive a review of the literature of the past 150 years as possible, we have been able to locate only twenty-eight cases of intussusception occurring during the first month of life (Table II).

ANALYSIS OF LITERATURE

An analysis of the twenty-eight cases is complicated by sketchy or deficient information in many instances.

1. *Age:* In only twenty-two of the twenty-eight cases was the exact age at the time of onset revealed. Of the twenty-two known, however, it is interesting to note that eighteen occurred during the first week of life.

2. *Sex:* Of the nine cases in which sex is known, five occurred in males.

3. *Maturity:* Of the nine cases in which exact information regarding maturity is available, eight occurred in full-term newborn infants and one in a seven-month premature infant.

4. *Symptoms:* Of the twenty-eight cases, only eight had adequate description of the symptomatology. Of these, vomiting and bloody stools occurred in all eight instances. Abdominal distention was found in three cases. Intermittent crying and drawing up of the legs was present in four instances. A normal meconium stool was described in four patients. Of the four infants with a palpable mass in the abdomen, two were found in the left side, one on the right side, and one felt per rectum. In none of the eight cases was diarrhea described.

5. *Type of Intussusception:* This information was obtainable in only six cases; two of each of the following types: ileocecal, ileocolic, and jejunojejunal.

6. *Treatment:* In only ten instances was the treatment described. Six of these patients underwent surgery with simple reduction alone in two instances and intestinal resection with anastomosis in four cases. The remaining four patients were treated nonsurgically and all died. The lone survivor of the patients treated surgi-

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TABLE I. INCIDENCE OF INTUSSUSCEPTION IN THE NEWBORN INFANT

AUTHOR	NO. TOTAL CASES	NO. NEWBORN INFANTS	INCIDENCE (%)
Gross[1]	702	2	0.28
Fitzwilliams[2]	1,000	1	0.10
Wansbrough and Cram[3]	575	1	0.17
Walton[4]	239	0	0.00
Monrad[5]	115	0	0.00
Ravitch[6]	152	1	0.66
Kahle[7]	151	1	0.66
Oberhelman and Condon[8]	107	1	0.93
Hogg and Donovan[9]	123	1	0.81
Koch and Oerum[10]	397	1	0.25
Mussil[11]	105	1	0.93
Perrin and Lindsay[12]	400	1	0.25
Hess[13]	314	2	0.64
Close[14]	363	0	0.00
Wakely and Atkinson[15]	121	1	0.83
Brown[16]	31	0	0.00
Gordan[17]	44	0	0.00
Ware and Coffey[18]	65	1	1.54
Magney[19]	56	1	1.78
Peterson and Carter[20]	64	0	0.00
Smith[21]	35	0	0.00
Moore[22]	43	0	0.00
Cleveland[23]	35	0	0.00
Mayo and Woodruff[24]	55	1	1.78
Gibbs and Sutton[25]	92	0	0.00
Robbins[26]	65	0	0.00
Peterson[27]	46	1	2.17
Thompson[28]	50	0	0.00
Clubbe[29]	144	0	0.00
Hirschsprung[30]	64	0	0.00
Hipsley[31]	51	0	0.00
Harper[32]	112	0	0.00
Bolling[33]	50	0	0.00
Total	5,966	18	0.30

TABLE II. CASES OF INTUSSUSCEPTION IN THE NEWBORN INFANT

CASE	AUTHOR	DATE	AGE	SEX
1	Jeffrey[34]	1944	1 da.	M
2	Scott[35]	1942	6 da.	F
3	Lewis[36]	1939	5 da.	M
4	Prouty et al.[37]	1948	2 da.	F
5	Tweedy[38]	1904	2 da.	?
6	Gross[1]	1953	3 da.	?
7	Gross[1]	1953	?	?
8	Fitzwilliams[2]	1908	?	?
9	Wansbrough and Cram[3]	1952	4 da.	?
10	Ware and Coffey[18]	1950	3 wk.	?
11	Magney[19]	1947	7 da.	?
12	Ravitch and McCune[6]	1950	?	?
13	Kahle[7]	1951	2 da.	?
14	Oberhelman and Condon[8]	1948	2 wk.	?
15	Hogg and Donovan[9]	1946	?	?
16	Mayo and Woodruff[24]	1941	24 da.	?
17	Koch and Oerum[10]	1912	7 da.	?
18	Mussil[11]	1944	?	?
19	Perrin and Lindsay[12]	1921	1 da.	?
20	Hess[13]	1905	6 da.	?
21	Hess[13]	1905	?	?
22	Dowd[39]	1913	5 da.	M
23	Peterson[27]	1922	6 da.	?
24	Gelston and Sappington[40]	1930	2 da.	F
25	Steele[41]	1916	4 da.	M
26	Wakely and Atkinson[15]	1938	3 wk.	F
27	Benson[42]	1951	1 wk.	?
28	Schiavone[43]	1936	9 da.	M

cally had resection with anastomosis. It is interesting to note that this surgical success occurred in 1913 and that four of the other five surgically treated cases have been described since 1939, the most recent being in 1948.

CASE REPORT

P. C., a newborn female infant, was delivered by normal spontaneous delivery to a para iv, gravida iv mother after an uneventful pregnancy and a normal labor. The blood of the mother was type B and Rh positive. The baby weighed 5 pounds, 2½ ounces at birth and measured 20 inches in length.

The infant was starved for a period of twelve hours, during which time she passed two normal meconium stools, and then was placed on sterile 5 per cent glucose in water feedings which she took poorly. Physical findings on the first day of life were normal, and at 24 hours of age, the baby was started on breast feedings, which she took poorly, despite the absence of vomiting and crying.

On March 2, 1954, at 30 hours of age, the baby suddenly passed a segment of gangrenous tissue through

the rectum. Slight taxis of the extruded portion caused separation of the slender membranous attachment above the view of the examiner.

Digital examination of the rectum after passage of the tissue revealed nothing abnormal, and examination of the abdomen revealed it to be soft and no masses were felt. The baby was in no distress and did not pass any blood per rectum. Hemoglobin at this time was 18 grams and the red blood cell count was 5.42 million cells per cubic millimeter. A flat plate of the abdomen revealed normal gas shadows in the small and large intestines seen as far as the rectosigmoid junction. No roentgenographic evidence of obstruction could be seen. Proctoscopy to 1½ inches revealed no abnormality or rectal bleeding. It was felt that the lower third of the sigmoid colon could be seen adequately during the proctoscopy.

After passage of the tissue, all feedings were withheld, and the patient maintained on parental fluids. Approximately eight hours later, the abdomen became distended and another film of the abdomen revealed distention of all intestinal loops, with no localization of the obstruction. The baby became dehydrated, and the hemoglobin rose to 19 grams. The bowel sounds which had previously been hyperactive were now more sluggish. A polyethylene catheter was inserted into the right saphenous vein and the fluid balance was corrected. A tube was passed into the stomach and Wangensteen suction started because of the onset of vomiting. During the next two days of life, there was no further stool or any rectal bleeding. By March 3, the third day of life, the abdomen was no longer distended. Lipiodol was instilled into the rectum and upon initial examination was only injected

Fig. 1.—Initial Lipiodol installation demonstrating a mass in the mid-transverse colon.

into the transverse colon because of insufficient radiopaque material available. There was no pathology in the rectum or left colon but a definite corkscrew mass was demonstrated in the mid-transverse colon which was resisting further injection of Lipiodol (Fig. 1). The Lipiodol instillation was repeated three hours later to a total of 80 c.c. At this time, the intussuscepting mass was again visualized in the transverse colon, and was

Fig. 2.—Repeat Lipiodol installation revealing obstruction of the distal ileum.

pushed ahead of the radiopaque stream, under fluoroscopic control, outlining the entire colon. The apex of the Lipiodol then terminated a short distance proximal to the ileocecal valve and outlined a point of complete obstruction (Fig. 2).

Shortly after the diagnosis was made and after the patient was prepared for surgery, she was brought to the operating room at 56 hours of age. Under general (drop ether) anesthesia, the abdomen was opened through a muscle splitting right rectus incision, and examination of the abdominal viscera revealed dilated jejunum and ileum, the latter ending in a bulbous point which was completely sealed off (Fig. 3). The ileal mesentery in this area (distal to the bulbous point) presented a V-shaped defect. The proximal 4 cm. of ileum was collapsed (as was the colon) and the proximal end of this distal ileum presented a concave surface. It appeared obvious that prior to reducing the intussusception by means of Lipiodol enema, the proximal ileum had inverted into the distal ileum which was also inverted into at least the proximal one-half of the large bowel. The closed ends of the ileum were excised, and an end-to-end anastomosis was performed using a continuous No. 00 chromic catgut suture as the inner layer, followed by a second row

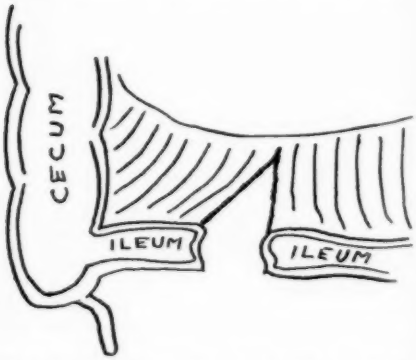

Fig. 3.—Diagrammatic sketch of defect in bowel and mesentery at the time of surgery.

of interrupted Lambert sutures using No. 0000 black silk. In excising the ends of the ileum, bias cuts at approximately 45 degrees were made, allowing a good anastomosis with ample internal diameter at the anastomotic point. The ileal mesenteric defect was closed, using interrupted sutures of No. 0000 black silk. The abdominal wall was closed in layers, using interrupted No. 0000 black silk sutures.

On the first postoperative day, the abdomen was soft and bowel sounds

were heard, with passage of several small brownish-black meconium-type sticky stools. The hemoglobin remained normal, and, on the next day, the tube was removed from the stomach without any distention. The patient was started on small quantities of sterile 5 per cent glucose in water feedings which were taken readily and retained. On the third postoperative day, the polyethylene catheter was removed from the leg and dilute milk feedings started. At this time the stools were normal. The patient began to gain weight and took the feedings in increasing amounts. Antibiotics were discontinued the seventh postoperative day and the sutures removed the following day. The wound healed normally. On March 29, twenty-six days after surgery, the baby weighed 5 pounds, 12 ounces at the time of discharge from the nursery unit. Follow-up examinations revealed no further vomiting, bloody stools, or symptoms of colic at any time. It is interesting to note, however, that the baby developed an eczema at 3 months of age, shortly after onset on solid foods, and cleared after the solid foods were discontinued and a soybean-type feeding instituted. The weight at 3 months was 8 pounds, 9 ounces.

Pathological examination of the specimen revealed an irregular, tubular-shaped mass measuring 8 cm. in length and varying in diameter from 0.6 cm. at the distal end to 1.2 cm. at the proximal end (Fig. 4). Approximately midway of the specimen, there was a marked indentation suggestive that the specimen had been constricted at that point. The distal four-fifths had a grayish-black coloration and was of a friable consistency, while the proximal one-fifth had a dusky, reddish-brown coloration and was more viable in appearance and consistency. The specimen was cut in cross section and sections were taken from the tip, mid-portion, and proximal region to be embedded for microscopic study. On microscopic examination, the sections taken from the tip and mid-portion showed only gangrenous tissue in which no viable structures could be recognized. The section from the proximal segment revealed tissue identifiable as small intestine. It appeared somewhat edematous and completely reversed its normal orientation in cross section, i.e., the mucosa was on the outside and the serosa was on the inside.

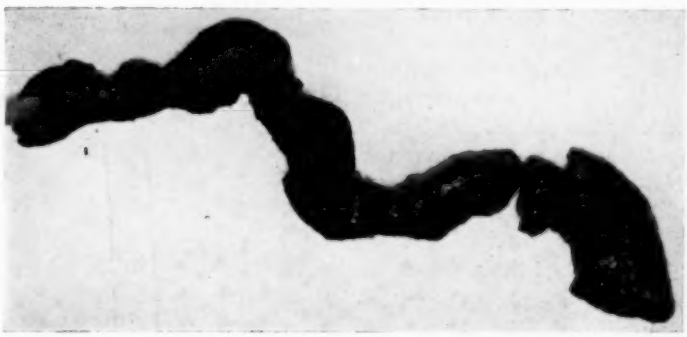

Fig. 4.—Gangrenous segment of bowel passed per rectum.

DISCUSSION

In the nineteenth and early portion of the twentieth century, many of the patients with intussusception were allowed to go to a "natural cure," in which cases the intussusception became necrotic and sloughed, passing

out the rectum, and was accompanied by spontaneous auto-anastomosis. Leichtenstern[44] in 1877 found that 42 per cent of the 593 cases of intussusception which he collected underwent spontaneous cure in this manner. The separation usually took place eleven to twenty-one days after onset of the disease. The separation occurred most frequently in the ileum and was rare to take place under the age of 2 years.

Since the passage of the segment of necrotic bowel occurred on the second day of life, it seems reasonable to assume that the intussusception had its origin on the first day of life, although the patient was asymptomatic during this period. It is certain the obstruction had its onset following birth, since air could be demonstrated in the large bowel as far as the rectosigmoid junction on roentgenographic study of the abdomen.

In attempting to explain the pathogenesis in our case, the theory put forth by Treves[45] in 1901 seems most logical. He described the pathologic process of spontaneous recovery in intussusception as occurring in two ways: Adhesions form between the peritoneal surfaces of the entering portion and the ensheathing portions of the intestine. If a separation takes place first at the end of the middle layer, the intussusceptum will straighten out at the apex. Later as separation takes place in the middle layer near the entering portion of the intestine, the section will be passed with its peritoneal layer outermost. A rarer type occurs if the separation takes place at the two ends of the middle layer in the reverse order; the section will be passed with the mucous surface outermost. The rarer type apparently occurred in our case since the mucosal surface was outermost. Ileal mesentery was obviously caught up in the intussusception and also became necrotic since at the time of operation, a V-shaped defect in this structure, adjacent to the bowel defect, was discovered. It is extremely interesting to us that at 56 hours of age (approximately forty-eight hours after onset of the intussusception) at the time of surgery, complete sealing of both ends of the ileum had occurred. The incorporation of the ileo-ileal intussusception into the colon undoubtedly prevented spillage of intestinal contents until healing had occurred.

Instillation of a radiopaque material under direct fluoroscopic control frequently is of great diagnostic value. Hipsley[31] was among the first who popularized such a procedure as a therapeutic measure as well. In our case, besides demonstrating the pathology, a reduction of the intussuscepting ileum was obtained to the point of a complete obstruction, which indicated the requirement for immediate surgery.

The case presented represents the first recorded instance of the passage of an intussusception per anus during the newborn period. Although in similar cases of this type intussusception, auto-anastomosis might well occur spontaneously, the result in the case at hand was complete obstruction on the terminal ileum.

By far the preponderance of intussusception cases in children will be encountered in the 6-to-18-month age group, and although it infrequently occurs during the first three months,

the pediatrician must always be aware that this condition does occur in the newborn period. With prompt recognition, early surgical correction, when such therapy is indicated, should markedly lower the mortality rate of intussusception occurring during the first month of life to levels comparable with results in the older age groups.

SUMMARY

This unusual case represents the twenty-ninth recorded instance of intussusception occurring during the newborn period. It was complicated by expulsion of the necrotic bowel per anus, terminating in complete intestinal obstruction, which required surgical correction and resulted in cure.

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JAUNDICE DUE TO HYPERTROPHIC PYLORIC STENOSIS

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JAUNDICE occurring in an infant only a few days or weeks of age presents a diagnostic problem to the physician which must be met promptly. There are numerous causes which may be quite varied and involve differing physiologic mechanisms, and in attempting to establish the correct diagnosis, each cause must be considered.

Physiologic jaundice, which occurs in approximately 50 per cent of all infants, begins between the first and fifth days of life and is usually gone by the end of the second week. Its frequent occurrence rarely offers any diagnostic difficulty. Jaundice due to erythroblastosis fetalis is accompanied by a severe hemolytic anemia and is apparent in the first few hours of life. Icterus due to sepsis ordinarily does not begin until the end of the second week. The accompanying illness is usually quite severe and is associated with other findings of infection. For the sake of completeness, catarrhal jaundice, homologous serum jaundice, congenital syphilis, and Weil's disease must be included, although these are extremely rare in the newborn infant.

Finally, obstructive jaundice must be considered as a cause for icterus in this age group. It is usually due to congenital atresia or absence of the bile ducts, or to inspissated bile. When congenital obstruction of the bile ducts exists, the jaundice may occur early or late in the newborn period, and becomes progressively more intense. The stools contain little or no bile. The bilirubin level is extremely high, and the van den Bergh reaction is direct. There is no improvement unless surgical correction can be achieved. When the jaundice is due to inspissated bile, the clinical picture is identical; however, it often can be corrected with medical management or it improves spontaneously.

We would like to introduce another cause for obstructive jaundice in this age group, hypertrophic pyloric stenosis. A fairly complete search of the literature has failed to reveal a description of this clinical condition.

CASE REPORTS

CASE 1.—The first case is that of a 7-week-old male infant, S. E., who was first seen on Sept. 17, 1953, because of jaundice and vomiting. History obtained from the parents revealed that this child was the product of the mother's second pregnancy. Jaundice was noted on the second day of life and this jaundice had not only persisted, but had become considerably more intense in the few days prior to examination. He had always eaten and gained well until one week before he came under observation. At that time, he began to have projectile vomiting and lost a total of one pound. In spite of the vomiting he had continued to be hungry and had taken feedings well. His stools had remained normal color but had become scanty in the few days prior to his first visit. A few stools had been very dark, and the mother stated, upon questioning, that they were actually tarry. He had had no fever.

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Physical examination revealed a vigorous baby who was not acutely ill. His temperature was normal. He was moderately dehydrated, but was very hungry and had a marked icteric tinge to his skin and sclerae. His back and neck were arched backward and held in this position most of the time. The liver was tender and enlarged about 2½ to 3 cm. below the right costal border. All other physical findings were normal. After hospitalization, considerable laboratory and x-ray work was carried out. This included a hemoglobin of 11.4 grams or 73.6 per cent, a white blood count of 7,600 with a normal differential, and a normal pylorus which is between 2 and 3 cm. in length. Only a very small amount of Umbrathor passes into the small bowel. . . . Conclusion: Hypertrophic pyloric stenosis."

On the day following admission, projectile vomiting continued and marked peristaltic waves were seen in the epigastrium. At that time, it was felt that a pyloric tumor could be palpated. Hydrating measures were instituted and the child was prepared for surgery.

On Sept. 19, 1953, the following operative procedure was done: Under ether anesthesia, the patient was prepared and draped in the usual manner.

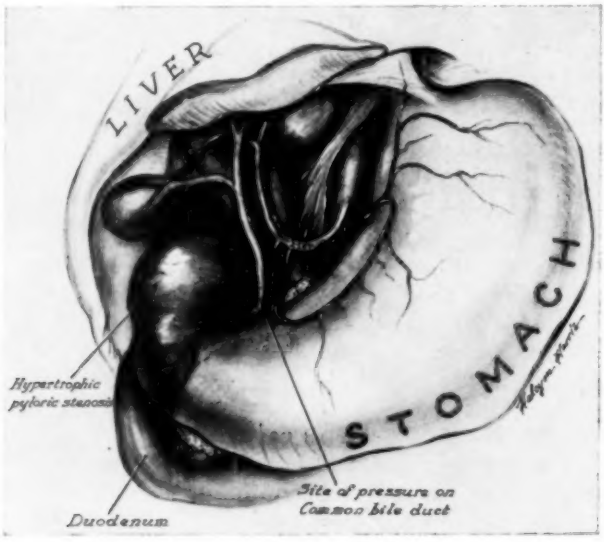

Fig. 1.—Drawing showing position of pyloric tumor in relation to the common bile duct.

routine urinalysis. The total serum bilirubin was 17.3 mg. per cent; 1.60 mg. or 9 per cent of the total bilirubin was directly reacting, and 0.60 mg. or 38 per cent of the directly reacting bilirubin reacted immediately. The cephalin cholesterol flocculation test was 1 plus at 48 hours. An upper gastrointestinal series was done and the following is quoted from the roentgenologist's report: ". . . A definite string sign is seen in the region of the

An upper right paramedian skin incision was made and developed through the subcutaneous tissue. The right rectus sheath was divided and the right rectus muscle retracted laterally. The peritoneal cavity was entered. Exploration revealed a somewhat dilated stomach with evidence of a thickened wall. The pyloric tumor was palpable in the depths of the wound. Further exploration revealed that the pyloric tumor was angulated posteriorly and

anchored around the lateral edge of the gastrohepatic ligament so that the pyloric tumor became incarcerated in the region of the foramen of Winslow (Fig. 1). The liver was slightly enlarged but had a normal appearance. The gall bladder and common duct were not grossly dilated. The pyloric tumor was manipulated free from the location previously described and brought up into the wound. An incision was made along the anterior surface of the tumor and developed down to the mucous membrane. This incision was then continued upward to the distal end of the stomach and downward to the duodenum, completing the conventional Ramstedt operation. The duodenum was not entered during the dissection. The abdominal wall was closed, using catgut for the peritoneum, silk for the fascia and skin.

The patient remained in the hospital until September 26, during which time he had an uneventful recovery, and there was rapid and complete disappearance of the jaundice.

Case 2.—The second case is that of a 5-week-old male infant, R. C., who was first seen on July 26, 1953, because of severe, persistent vomiting of two weeks' duration. He was the third child in the family, but the first son. He was a large baby and had done very well until the present illness. The vomiting was projectile, of increasing severity, and since its onset the baby had lost 12 ounces. At the time of examination, he was urinating infrequently and having scanty stools. He had become quite restless during the few hours before admission to the hospital.

Physical examination revealed a well-nourished male infant who was moderately dehydrated. There were marked peristaltic waves passing from left to right across the epigastrium. A definite pyloric tumor was palpable in the right side of the abdomen and projectile vomiting occurred during the course of the examination. The only other abnormality noted on this original examination was the presence of mild but definite icterus. This was observed both in the scleras and the skin. The presence of this jaundice had not been a cause of great concern for the parents of this child and had not been mentioned in the history, but when they were questioned about it, they stated that they, too, had noticed that the baby was yellow and had been so for about a week.

Laboratory studies in this case were held to a minimum because of financial considerations. A complete blood count was normal and bleeding and clotting times were within normal limits. Urinalysis was normal.

Following admission of the infant to the hospital, hydrating measures were instituted and an attempt was made to control vomiting by use of atropine and sedatives. This was unsuccessful, and, as this child was watched over a period of approximately thirty-six hours, it became quite evident that in spite of the icterus, the diagnosis of pyloric stenosis was well justified by the presence of marked peristaltic waves and the palpation of a pyloric tumor. He was therefore prepared for surgery.

On July 28, 1953, under ether anesthesia, a right paramedian skin incision was made in the right upper quadrant and developed through the anterior sheath of the rectus. The rectus muscle was retracted laterally and the peritoneal cavity entered. The stomach was dilated and filled with air, which was removed by aspiration. Exploration revealed an obvious pyloric tumor which was angulated around the lateral edge of the gastrohepatic ligament, producing pressure on the common duct just above the pancreas. The gall bladder was not enlarged and the extrahepatic biliary passages appeared to be of normal size. The liver was not grossly abnormal. The pyloric tumor was manipulated free from its incarcerated position and brought up into the wound. An incision was made in the pyloric muscle near the gastric end and developed downward to the mucous membrane. The incision was continued downward toward the duo-

denum and the musculature spread so that the mucous membrane could bulge throughout the extent of the wound, conforming to the Ramstedt procedure. The duodenum was not entered during dissection. The wound was closed in layers using catgut for the peritoneum, silk in the fascia and skin.

Following surgery this baby did very well. His recovery was practically uneventful. There was an occasional episode of vomiting which diminished in frequency during the immediate postoperative period. The jaundice disappeared promptly and could not be detected by the time of discharge from the hospital on the seventh postoperative day. Following his release from the hospital he continued to improve, gained weight well, and has had no recurrence of the symptoms which could be related to this illness.

Fig. 2.—Upper gastrointestinal x-ray of first patient showing unusual angulation of pylorus.

COMMENTS

Following the experience with these two cases of pyloric stenosis with jaundice, we reconsidered the clinical data in an effort to establish some specific differential point which would assist in making an accurate preoperative diagnosis. In reviewing the x-rays of the first case, an unusual appearance was noted which might serve as a diagnostic aid. It was observed that the pylorus was angulated sharply posterior in an arc to the left (Fig. 2) in contrast to the usual transverse position of the pyloric canal in hypertrophic pyloric stenosis (Fig. 3). Perhaps this roentgen appearance is diagnostic of the clinical condition herein

Fig. 3.—Upper gastrointestinal x-ray showing the typical position of pylorus in hypertrophic pyloric stenosis.

described, although we are reluctant to draw definite conclusions without additional cases.

The observations made at the time of surgery convinced us that the unusual angulation of the pyloric tumor was responsible for extrinsic pressure on the common bile duct, sufficient to produce jaundice. This conclusion is further supported by the fact that the pyloric tumor was wedged in position and could be freed from its posterior location only with considerable difficulty.

SUMMARY

Jaundice as a complication of hypertrophic pyloric stenosis is described.

The anatomical cause for this finding is demonstrated.

The differential diagnosis of jaundice in the neonatal period is reviewed.

Two illustrative cases are presented.

It is suggested that a characteristic x-ray appearance may be found in this situation.

Obstetrical Notes

We hear from Prince Georges County in Maryland, that sometime in July last a Negro Woman belonging to Mr. Thomas Clarke of that Place, Lawyer, was deliver'd of a Monster with two Heads, one yellow and the other black, looking from each other, the Sex indistinguishable. It liv'd but a few Minutes.

AMERICAN WEEKLY MERCURY, September 16, 1742.

The wife of Mr. Enoch Tuells, of this City, was this week delivered of her fourth pair of Twins in Succession; she is now 29 years of age—has been married 11 years, and has had 15 Children. Mr. Tuells is only 34 years of age—a healthy, active man. *What a prospect!*

We hear from New-Rochelle in West-Chester County that a Negro Woman belonging to Mrs. Rodman of that place, was last Week deliver'd of a negro Child, after which she continued as well as Women in her Circumstances generally are, for 3 or 4 Days, when she was taken in Labour again, a deliver'd of a Mulatto Child.

CONNECTICUT COURANT, March 17, 1766.

A CASE OF MEGALOBLASTIC ANEMIA ASSOCIATED WITH STEATORRHEA AND THE CELIAC SYNDROME

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ZUELZER and Ogden[1] in 1946 reported twenty-nine cases of a macrocytic anemia, designating the syndrome "megaloblastic anemia of infancy."

The cause of megaloblastic anemia of infancy cannot be attributed to any single etiological factor. The pathogenesis appears to be an interference with the maturation of the red cell elements, so that characteristically immature members of the erythrocytic series are observed.[2] Several explanations have been advanced for this aberration. The most plausible one appears to be that of a dietary deficiency or avitaminosis.[3] Folic acid and citrovorum factor (folinic acid) are directly responsible. Vitamin C and vitamin B_{12} also have a role in this process. They have not been as effective as folic acid, however, in curing this blood dyscrasia.[4]

Evidence has been advanced indicating that folic acid and vitamin C are essential for the production of citrovorum factor.[5] The latter is specific in the formation of mature erythrocytes. Folic acid is an essential nutrient for the maturation of bone marrow and the synthesis of nucleoproteins. These proteins are found in all developing cells including those of the blood. The bone marrow is directly affected by the deficiency of folic acid, folinic acid, and vitamin C, resulting in an inability to produce mature red blood cells.[5]

Wintrobe[4] suggests that those cases reported as goat's milk anemia are similar to those described by Zuelzer and Ogden.[1]

Macrocytic anemia is seen in pernicious anemia, celiac disease, liver disease, and in malformations of the gastrointestinal tract. Megaloblastic bone marrow is observed in these syndromes.[6]

A case of megaloblastic anemia is reported because of several unusual features. These included a celiac syndrome and steatorrhea which are rarely found in this type of anemia. The onset of symptoms was at a later age than is usually observed.

CASE REPORT

J. R., a 2-year-old Puerto Rican male child, was admitted to the Morrisania City Hospital on Aug. 27, 1946, with a three-month history of diarrhea, vomiting, anemia, anorexia, irritability, and generalized edema of gradually increasing intensity. His diet consisted primarily of rice, milk, and chicken. Meat and other foods had been excluded. The developmental history was essentially normal.

Physical examination disclosed a markedly pale child, who appeared chronically ill. The blood pressure was 100/72 mm. Hg, temperature 98.6° F., pulse 22 beats per minute, and the weight 12.3 kilograms (birth weight 4.5 kilograms). Generalized edema

From the Pediatric Service of the Morrisania City Hospital, Dr. Harry D. Pasachoff, Director; and the New York Medical College.

was most marked in the periorbital area and in the lower extremities. Ascites was noted. The liver and spleen were not palpable.

The blood count on admission revealed the following: hemoglobin 4 Gm. per cent; red blood cell count 1.24 million per cubic millimeter; white blood cell count 4.3 thousand per cubic millimeter, with 54 per cent granulocytes and 46 per cent lymphocytes. Three hundred cubic centimeters of whole blood was given. An increase in the hemoglobin to 8 Gm. per cent and in the red blood cell count to 2.5 million per cubic millimeter resulted. No reticulocytes were seen in the peripheral smear. Bone marrow examination showed a very cellular marrow, with 64 per cent megaloblasts. The granulocyte series was normal.

The peripheral blood smear suggested macrocytosis. The peripheral red blood cell volume index was 0.9. Gastric analysis revealed free hydrochloric acid 20 degrees (normal 0 to 30 degrees), and total acid 65 degrees (normal 10 to 50 degrees).

Duodenal drainage disclosed normal trypsin and amylase levels.

Vitamin A determinations indicated poor absorption of vitamin A as demonstrated by a maximum rise of only 11 units.

The glucose tolerence test, after giving 12 Gm. of glucose, revealed a flat curve.

The cephalin flocculation was one plus. Blood chemistries were as follows: total protein 5.9 and 6.9 Gm. per cent; the albumin in the latter determination was 3.92 Gm. per cent and the globulin 2.99 Gm. per cent, with an albumin-globulin ratio of 1:3. The nonprotein nitrogen was 21.6 Gm. per cent, urea nitrogen was 13 mg. per cent, cholesterol 109 mg. per cent, cholesterol esters 61 mg. per cent. The blood Wassermann was negative.

Blood agglutination tests for typhoid, typhus, and brucella infections were negative. Urinalyses were repeatedly negative. An electrocardiogram was negative. X-rays of the chest, skull, and long bones did not reveal any pathology. Fluoroscopy gave evidence of slight enlargement of both ventricles.

Despite thiamine, brewer's yeast, and ascorbic acid therapy, the child remained pale, listless, and edematous. He had four to five loose, bulky, foamy, foul stools daily. A transfusion of 300 c.c. of whole blood had been given on August 28, without permanent effect. On September 13 folic acid therapy was instituted, with 15 mg. given intramuscularly daily. At this time, the reticulocyte count was 0.9 per cent.

On September 18 the bone marrow again showed marked hyperplasia of the erythrocytic elements, but the red blood cell series now revealed a greater degree of maturation, in that normoblastic elements predominated over the megaloblastic elements. This maturation was not seen in the peripheral blood picture, which disclosed a more severe anemia, but the reticulocyte count had risen to 10.5 per cent, at which level it persisted for one week, and then gradually declined to 0.5 per cent.

The patient clinically was markedly improved, so that by September 30 he had become completely asymptomatic except for the foul, bulky stools which persisted. At this time the peripheral blood and the bone marrow both revealed almost completely normal findings.

The hemic components had risen on folic acid therapy, and the hemoglobin was now 12.5 Gm. per cent and the red blood cell count was 5 million per cubic millimeter.

The stools continued to be foul, acid, loose, and voluminous. Examination of the stool disclosed the following: the culture was negative for known pathogens; fat was noted in excess; carbohydrate was present in normal amounts; the reaction was acid. Repeated stool examinations were not remarkable except for the steatorrhea.

On October 29 parasites were observed for the first and only time, despite subsequent frequent stool examinations. There was a mixed infection of *Giardia lamblia* and *Endolimax nana*.

HEMOGLOBIN
gram.
RED BLOOD CELLS
million
RETICULOCYTES
percent
DAYS
WHOLE BLOOD
500 cc
THIAMINE CHLORIDE
100 mgm. I-M
FOLIC ACID
1 mgm. I-M
VITAMIN B COMPLEX

FIG. 1.

A modified celiac diet was instituted on November 18. This included fat-free protein milk with banana powder, pot cheese, scraped beef, hard-boiled egg white, and bananas. On this regimen, the stools improved, and the steatorrhea was under control. When the patient was discharged on Dec. 8, 1946, the evacuations were less frequent, and their consistency quite normal.

A transfusion of 300 c.c. of whole blood had been given on August 28. Folic acid (15 mg. intramuscularly) was started on September 13 and continued daily until October 5; it was reintroduced on October 14 and continued until November 4. Other therapy consisted of the daily use of thiamine chloride 100 mg. intramuscularly, vitamin B (Cowley) 4 tablets, and ascorbic acid 200 mg. (Fig. 1).

A follow-up examination was conducted and an interim history was obtained on Sept. 25, 1953. During the seven-year period which had elapsed since his discharge from the Morrisania City Hospital, no steatorrhea was present, despite the fact that all types of food were included in his diet. No food intolerence was noted. Stools were usually brown and well formed. The patient tended to be constipated and required the use of cathartics more frequently than other members of his family. At the age of 9 years, he was 129.5 centimeters tall, weighed 30 kilograms, was active and alert, and appeared to be in good health. The blood count was as follows: hemoglobin 13.2 Gm. per cent; red blood cell count 4.8 million per cubic millimeter; white blood cell count 6 thousand per cubic millimeter, with 73 per cent polymorphonuclear leukocytes and 27 per cent lymphocytes; bleeding time 25 seconds; clotting time 2 minutes 15 seconds. A stool specimen was brown, formed, and showed a trace of fat qualitatively. Quantitatively, there was 4.2 per cent of total fat. No ova or parasites were present.

DISCUSSION

This child presented a clinical picture compatible with a diagnosis of megaloblastic anemia. He exhibited pallor, irritability, anorexia, generalized edema, vomiting, and diarrhea. The physical examination did not disclose any splenohepatomegaly, petechiae, or evidence of scurvy, which have been noted in cases previously reported.[1]

This disease is usually observed in infants between 2 and 16 months old.[13] Our case is unusual in that the onset of symptoms was at 21 months of age.

The association of steatorrhea and the celiac syndrome with megaloblastic anemia is unusual.[11] The prompt hematologic response to folic acid therapy as evidenced by definite reticulocytosis, maturation, and normal development of the red blood cell series was obvious. The bone marrow paralleled this reaction and became completely normal, with a disappearance of the megaloblastic arrest.

The steatorrhea and gastrointestinal symptoms persisted for several weeks after the bone marrow and peripheral blood returned to normal. The stools became formed and normal in fat content after the child had been maintained on a celiac diet for a comparatively short time. The subsequent course of this boy would indicate that the celiac syndrome was a manifestation of the megaloblastic anemia. After his discharge from the hospital, the patient was permitted a free choice of diet, and for a seven-year period had no recurrence of the steatorrhea. Steatorrhea and celiac disease would not be expected to subside so abruptly; on the contrary, relapses are the rule.[7] Folic acid reversed the bone marrow dysplasia very promptly. The gastrointestinal symptoms were more refractory to therapy.

G. lamblia was detected in the stool of this patient on only one occasion. This parasite is known to be responsible for a diminution in vitamin A absorption.[8] The pathogenicity of this parasite is a controversial subject. Veghelyi[14] in a report from Hungary described several cases of giardiasis in which abdominal complaints, microcytic anemia, celiac syndrome, and retarded development were observed. The American literature, however, does not support the contention that *G. lamblia* is pathogenic in the human being.[9]

This is the first instance of megaloblastic anemia seen on our pediatric service in approximately 23,000 admissions over a period of twenty-six years. Our experience appears to coincide with that of the other clinics in the northeastern area of the United States, where there is a paucity of this syndrome.[10] We suggest that some other factor, still unknown, would explain the higher incidence of this disease in other localities.[12]

SUMMARY

A case of megaloblastic anemia with clinical and laboratory evidence of an associated celiac syndrome has been presented. Prompt hematologic response to folic acid therapy was achieved. Complete restoration of normal gastrointestinal function followed only after the reversal of the dysplasia of the bone marrow.

Observation of this child over a period of seven years has verified that the celiac symptoms and steatorrhea were manifestations of a nutritional deficiency of folic acid.

The low incidence of this blood dyscrasia in the northeastern area of the United States as contrasted with the higher incidence elsewhere is noteworthy.

We wish to acknowledge the assistance of Dr. Harry Wallerstein, Consulting Hematologist of the Morrisania City Hospital.

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THYMIC TUMOR OF THE PHARYNX

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THE presence of aberrant thymus above the level of the thyroid gland is rare. This report describes an infant in whom thymic tissue was found in the hypopharynx. A probable embryologic explanation of the anomaly will be presented.

CASE REPORT

The patient was a 3-week-old infant who was brought to the emergency room because the mother noted the appearance of a mass protruding from the mouth when the baby regurgitated. This had the general appearance of a second tongue, being about 1 cm. in diameter. The mass projected from the mouth for a few minutes and then disappeared into the mouth.

First examination failed to reveal the presence of the mass in the mouth or pharynx. Continued observation showed the mother's description to be accurate. The mass was then seen as shown in Fig. 1. There was also micrognathia. No other abnormalities were found. The child ate well, with no significant obstruction even with the mass inside the esophageal lumen. X-ray examination with barium showed the mass to be alternately swallowed and regurgitated (Fig. 2).

Direct laryngoscopy without anesthesia showed the base of the mass to be in the left hypopharynx, in the medial portion of the pyriform sinus. A suture was carried down to the pedicle and tied. The mass was then removed with a nasal snare. No bleeding occurred.

No further symptoms were noted and the infant progressed well without complications. Later fluoroscopy and esophagoscopy revealed a normal-appearing esophagus. After one year the child exhibited no sequelae.

Pathologist's Report.—The fresh specimen consisted of a small piece of tissue 3.5 cm. in length and 1 cm. in diameter (Fig. 3). The tissue was covered by a pink membrane and appeared soft. Cross-section revealed the interior to be made up of cords of yellow tissue set in pink membrane (Fig. 4). Sections showed a polypoid structure consisting of isolated groups of thymic tissue containing Hassall's corpuscles (Fig. 5.) Each lobule of thymic tissue was widely separated by fibroadipose stroma. In most places, the surface was lined by stratified squamous epithelium. In others it appeared lost and ulcerated. In places, the surface epithelium had grown downward in the form of irregular slender cords. Diagnosis: Hamartoma of the pharynx.

Fig. 1.

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Many benign tumors have been described in the pharynx and esophagus, grossly resembling the above lesion. Myxofibroma,[1] adenoma,[2] and polyp[3] have been identified. Chitty[4] describes a polyp in an adult which showed the same clinical picture as our patient. Reeves,[5] Potts,[6] Myers and Bradshaw,[7] and Franklin[8] have reviewed benign tumors of the hypopharynx and esophagus but found no instance of thymic tumor. Cysts of the epiglottis and base of the tongue are sessile and do not show the mobility exhibited by this pedunculated tumor.

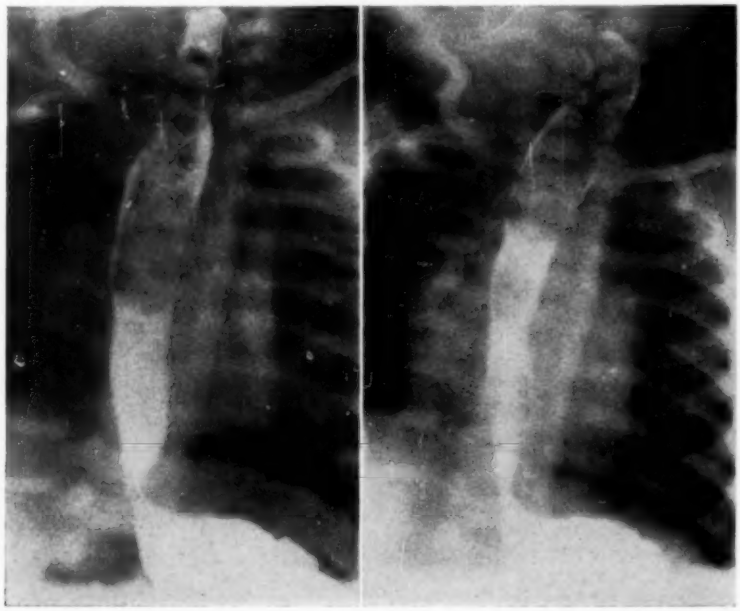

Fig. 2.

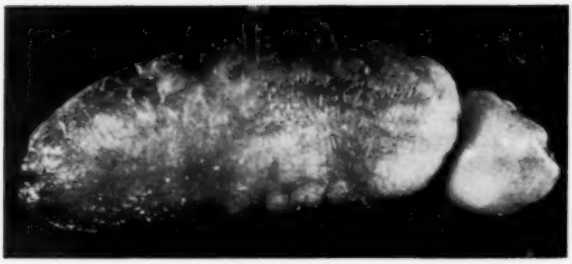

Fig. 3.

The presence of thymic tissue above the level of the thyroid gland is not difficult to explain since the thymus originates from the third and fourth branchial clefts.[9] Gilmour[10] found that

in the 16.5 mm. embryo (about seven weeks) pouch complex IV includes a tubelike thymus connected with the pharynx. In the 18 mm. embryo the thymus IV has lost its connection with the pharynx. Persistence of thymus IV was found in 25 per cent of newborn infants. In such cases the thymus was always dorsal to the middle of the posterior border of the thyroid gland. It is probable that our case represents an instance in which a

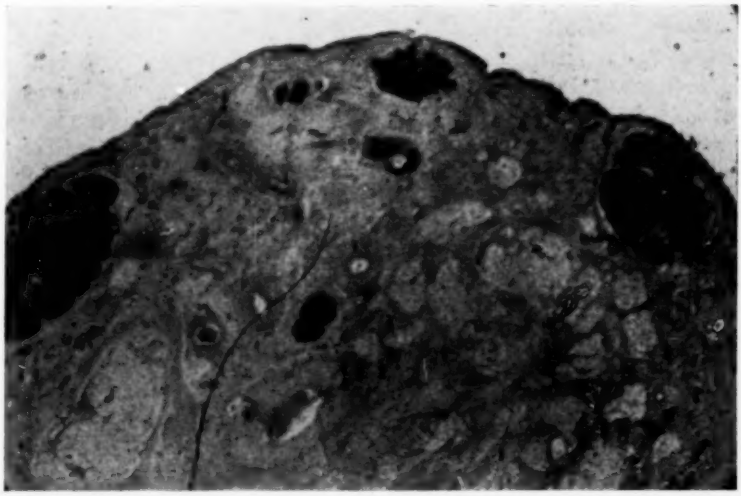

Fig. 4.

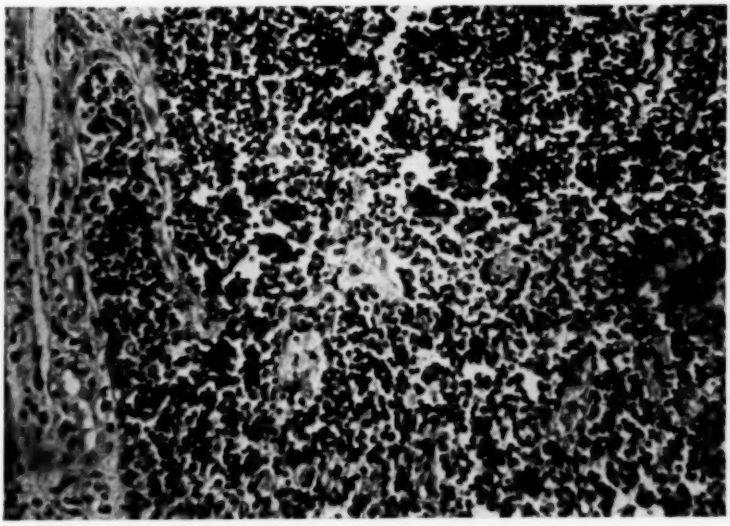

Fig. 5.

tubular thymus IV has persisted, retaining the connection with the pharynx which Gilmour observed in the 16.5 mm. embryo. Corroboration of this view is found in the fact that the location of the tumor corresponds exactly to the position of the fourth visceral cleft[9] in the hypopharynx. Since ossification of the first or mandibular arch also becomes evident in the 16.5 mm. embryo, it is not surprising that this infant also showed micrognathia.

SUMMARY

A case of pedunculated thymic tumor of the hypopharynx in a 3-week-old infant is described. A probable embryologic origin from the fourth visceral cleft is presented. Surgical removal was followed by an uneventful course.

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Medical Progress

TRENDS IN PEDIATRICS

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TO SEE ourselves as others need us (if we may take liberties with Bobbie Burns) would be an asset to every individual or group of individuals who purports to provide personal services for others. Such an attribute is particularly desirable for us as doctors for children. And with little risk of being wrong, it might be added that no medical group makes a greater attempt at self-evaluation.

The title of this presentation may convey the idea that I have definite chartings for the course which lies ahead or at least know in a general way the course or courses which should be followed. I would hasten to disillusion anyone who has such preconceived ideas. Perhaps my paper might be more appropriately titled, "a limited appraisal of pediatrics," to the end that questions pertinent to improvement in the medical care of children might be brought out. At any rate, if thinking is stimulated which will define some of the problems more clearly, then this presentation may to some extent be justified.

Measured in years, pediatrics as a specialty of medical practice may be considered comparatively young. Measured in terms of growth and development or by its index of achievement, a rating above its chronologic level would generally be accorded—at least by pediatricians.

At the turn of the century, pediatrics could be compared to a fairly lusty infant who had survived the rigors of the newborn period. It was the prevalence of serious illnesses among infants and young children and the high mortality rates in these age groups which were responsible for the emergence of the pediatrician. In these years the pediatrician had time for little besides disease. In areas of this country where births and causes of death were registered, the infant of 1900 had one in five chances of dying in his first year of life. If he survived the hazards of being born, he still had about one in six chances of succumbing to disease within his first year of life. If he survived this first year, he was far from being out of danger of lethal agents. Respiratory and intestinal infections, with no really adequate measures for their control, continued to be readily available to him—and his low rate of survival from them was not a credit to the medical profession. From an early age he was exposed to the so-called common contagious diseases, and he did not compete well with diphtheria or even with scarlet fever, measles, or pertussis. Even though the automobile was not an important lethal agent in 1900, accidents, the leading killer of children

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today, took more lives of infants and children then than they do at present.

All of these lethal agents were aided and abetted by a variety of contributory factors, which included poor physical hygiene, socioeconomic factors and nutritional disturbances, both general and specific. In the last category were rickets, scurvy, the various vitamin B deficiencies, and iron-deficiency anemia. Mere survival of infancy and childhood during these years was in itself an achievement, and survival without physical or mental defect was even more of an accomplishment.

Thus there were reasons why the pediatrician had little time except for disease. As further evidence of his preoccupation with the physical side of medicine, even his textbook of that day (Holt, 1898) contained no material on the evolution of behavior patterns in the growing child nor of the behavior deviations which today plague not only the parent but the child's doctor as well.

Within the period of the past half century, the pattern of pediatric practice has changed materially. The marked decrease in the incidence of acute illness now permits the pediatrician to spend the bulk of his time in the management of minor ills, the prevention of disease, and in guidance in child development and family living —perhaps better termed "how to live with Junior"—if looked at from the parent's standpoint, or, if from Junior's—"how to straighten out mom, pop, and the schoolteacher."

The character of pediatric practice varies from practitioner to practitioner and from one section of the country to another. Yet the similarities far outweigh the differences.

Most pediatricians can be placed in one of two categories: private practice and the academic field. To be sure, many pediatricians in private practice participate in teaching programs and some are involved in research; and some of those whose principal responsibilities are in the academic field devote a portion of their time to private practice.

The pediatrician in private practice is in the broad sense a general practitioner for children. This is as it should be, for it is in the area of family counseling that the pediatrician may well be making his greatest contribution. The opportunity for this type of service is a natural consequence when the physician assumes full medical responsibility for the children of the family.

The question naturally arises—"What is the role of the general practitioner in regard to child care?" In all sections of the country, even in those with the highest concentrations of pediatricians, more children receive their medical services from general practitioners than from pediatricians. Furthermore, even though the pediatrician spends a proportionately greater amount of his time in providing what may be termed preventive pediatric services, the general practitioner provides the bulk of such services. It could be expected, and certainly hoped, that there are qualitative differences in the majority of instances which would give preference to the services provided by the pediatrician. This situation points up what is perhaps the most important problem relative to the medical care of children at the moment.

TRAINING FOR THE CHILD'S PHYSICIAN OF TOMORROW

Should all pediatric care be provided by pediatricians? Should we encourage an increasingly larger proportion of medical school graduates to secure specialized pediatric training? If such is to be the decision, should we discourage, play down, or make no special provisions for improved training of the general practitioner in pediatrics?

Realistically, it will not be possible to train enough pediatricians to provide medical care for even the majority of children in the foreseeable future, even if such a course were deemed desirable. If this conclusion is accepted, what then should be done in regard to the training of the general practitioner—the one now in practice as well as the one as yet untrained?

Should there be developed a new type of practitioner—one who might be termed a family practitioner rather than a general practitioner? Certainly the title carries connotations and implications which seemingly are pertinent to the present situation. There is a growing realization that the family—the basic unit of society—is being confronted with a variety of factors stemming from the complexities of modern living, not only in cities but in rural areas as well, which tend to draw its members, adults and children, into outside activities and to weaken their relationships with one another. What can the physician do to assist in strengthening the family as a social unit and thus provide for children the stability which they need so much during the years of growth and development?

There are *those* who suggest:

—that the need for the pediatrician is almost over,

—that in large measure he has served his function by demonstrating the need for and the advantages of specialized medical care for infants and children,

—that within the near future his job can be taken over by the family practitioner of tomorrow—who would be skilled in the art and trained in the techniques of individual and family counseling and who also has medical training adequate for the majority of man's medical needs in the fields of internal medicine, pediatrics, and obstetrics,

—that specialized training in the field of pediatrics should be limited to the training of a relatively few in the subspecialties of pediatric medicine as, for example, in hematology, cardiology, or psychiatry. Such physicians would be located in metropolitan areas and especially in medical centers attached to medical schools where they would be available not only for consultative services but for teaching and research.

The assumption that the pediatrician as we know him today has in large measure fulfilled his mission and that he can and should be replaced by the family practitioner might be likened to the situation of certified milk in the milk industry. It is true that the introduction and continued availability of certified milk has been a big factor in the very great improvement of all market milk in this country. It is also true that there are now adequate safeguards in most communities to maintain a safe milk supply without the competition of certified milk.

No informed person will question that the pediatrician has had a significant part in the marked improvements in child health during the past twenty-five to fifty years. Parenthetically, it might be added that most pediatricians would give much of the credit to others—the bacteriologist, immunologist, sanitary engineer, chemist, pharmacologist, the educator, psychologist, and psychiatrist. Furthermore, most pediatricians recognize that not all of their efforts are successful or even correctly applied. There would seem to be little doubt that on occasion psychologic disturbances of parents and their children are aggravated by the pediatrician and some of them may even have their origin in him. However, it does not seem likely that the pediatrician who carries on a general practice among children is dispensable now or will be in the foreseeable future. Pediatries as a specialty is just coming of age rather than having fulfilled its mission, and efforts should be directed toward making the specialty a more effective one, perhaps better stated—making the medical care of children more effective. This latter is more appropriate since I think it is agreed that the pediatrician cannot now or in the future render all the general health services required by children.

If medical care for children is to become increasingly better, it will be due principally to constantly improved training programs which take into account the end product—the practitioner. This point of view does not imply that the intern or resident physician in training, or even the medical student, cannot or should not provide service to patients. They must participate actively in medical services. There are no other demonstrated means for gaining the necessary experience or the eventual sense of competence for the assumption of responsibility in medical practice. What is required is adequate teaching supervision graduated to the needs of the developing undergraduate, intern, and resident in the out-patient department and on the wards of the hospital. Stated in another way, the institution which accepts interns and residents must assume responsibility for their training and must not exploit them.

The Goal of Pediatric Practice.—At this point it may be in order to attempt to define the goal of pediatric practice. In the broad sense, it is to assist the child to become an adult able to compete at a level approaching his optimal capacity and to assume his share of responsibility within the community. Such a definition takes into account the varied natural abilities and potentials of individual children. It also suggests one of the serious problems confronting those interested in child welfare, namely, the avoidance of undue stress and pressure in schoolwork, athletics, and social activities. All too frequently the child is the victim of parental overambitions and the desire to derive reflected glory from the child's accomplishments. Often failures or disappointments of the parents in their own careers are the motivating factors for transferring or developing the sense of keeping up with the Joneses in their children at an early age. But whatever the factors may be, the child's physician must take time to find out the true nature of the child's environment, if he is to be a competent adviser to the child,

his family, and his school. There are no means for estimating the relative importance of the physician's role in the child's development; it differs from child to child. Most effectively it modifies and complements the activities of others who together form a sort of team to assist the child in his journey to adulthood. This team consists of the child himself, his family, his colleagues, his teachers, and a variety of persons who are involved in community services, the hospital clinic, the social worker, family welfare agencies, and, on occasion, the judiciary.

Nothing has been said concerning the provision of physical health services—preventive, supportive, and curative—simply because they represent the more obvious responsibilities of the physician. Special considerations are in order, however, for physically and/or mentally handicapped children. The reduction in the amount of acute serious illnesses among infants and children has made it possible to give more consideration to this group. In certain respects the layman, however, would appear to be ahead of the physician, at least in what is expected in the way of therapeutic results. There is a great need for a balance between optimism and realism, and the physician has a tremendous responsibility at the moment to see that handicapped children are given every possible opportunity but are not exploited, and particularly to see that the parents—and the child when possible—are not led to expect something which is not attainable. Rather it is essential that parents are given a realistic appraisal, continued guidance and therapy appropriate for their *particular* child. Whenever possible, handicapped children should be incorporated into regular school programs, and the physician must assume responsibility within his community to encourage schools to accept such children.

"How can an adequate supply of physicians for children be obtained?" Without professing to have an absolute answer or even original suggestions, it is proposed that we continue to train *pediatricians for general practice among children*, obviously of an increasingly better quality, and *pediatricians for academic pursuits and specialized services* to be rendered largely within medical centers for children, and that educational facilities be made adequate for the training of *family practitioners*.

The Pediatrician.—The practicing pediatrician must assume much of the responsibility for the quality of medical care of children, not only that which he provides directly, but also by such indirect means as setting standards within his community which serve as a bellwether or guide to other practitioners, by contributions to his local medical meetings, and by participation in the various community activities related to child development and health. His training must be adequate. If he is to function at a level above that of the trained "family practitioner of tomorrow," it is probable that he would be materially benefited by a minimum of three years of post-intern training, instead of the two now required by the American Board of Pediatrics in partial fulfillment of the requirements to be examined for certification. His training should provide a broad experience in general pediatrics including pre- and post-operative management of surgical pa-

tients and sufficient training in diagnostic technical procedures, as, e.g., in cardiology, neurology, and hematology, to permit him to serve as a consultant within his own community. Experience in child guidance and in family counseling should be integrated throughout the entire period of training. Although there are advantages in securing training from more than one medical center, it would seem desirable to spend a minimum of two years in one institution. There are many advantages, not the least of which is the opportunity to observe the children of a particular family for a minimal period of two years. Resident physicians who choose to spend three or more years in post-intern training have a variety of possibilities for their third, and, if elected, subsequent years. These possibilities include chief residencies, a regular residency or fellowship in one of the subspecialties, often with an opportunity to participate in research. Another possibility is a residency during the third year of training in a general or community hospital which has an excellent pediatric service but does not have the highly developed organization of the medical center. This type of service permits the resident considerable responsibility and an opportunity to test his training of the first two years.

The pediatrician in general practice may or may not have a special interest in any of the subspecialties of pediatrics. The desirability for such a tangent depends on the individual's philosophy, curiosity, and whether he is willing to expend the time and energy to secure special competency in his special field of interest be it allergy, metabolism, cardiology, psychiatry, or any one of the subspecialties of pediatries. For certain physicians such special interests are essential to satisfy their inner selves and often serve effectively as hobbies. When interest and training in a subspecialty become the dominant interest, the physician will rarely be able to find an adequate outlet for his talents outside of a metropolitan area and usually at the moment in organized medical centers, which may or may not have a close liason with a medical college.

The need for pediatricians in the academic field is limited but very real and is far from being of secondary importance. Most medical schools have need for a greater number of full-time teachers than they now have. There is no intent to underestimate the importance of the practicing physician in the teaching of pediatries, but the basic program should be established with full-time teachers and supplementation provided by paid and volunteer part-time staff members. In the full-time group there is a real need for pediatricians with broad training and interests. This factor is at times overlooked in the organization of a teaching department, and principal emphasis is placed on personnel who are highly trained in subspecialties. Such personnel have an important place in pediatric departments, but there is no reason why they cannot also have broad interests in pediatries. Some do. The point is simply that under ideal circumstances a teaching department should be nicely balanced with some members whose interests are in the general field and some whose interests and training are in the various subspecialties. Service to patients is essential in the teaching unit to provide experience for medical

students, interns, and residents. Research is essential not only for the potential of adding to existing knowledge but also for the stimulus which it provides to all who participate in the learning program—student and teacher.

The Family Practitioner.—The development of the family practitioner type of physician must begin in the medical school and continue throughout the hospital training period. It may well be that the greatest need in medical education at this time is a program which is adequate for such training. For too long a time the standards for general practice have been set at too low a level. Even an internship is not required in some states of this country, and though there are a few residencies designated for training in general practice, most of these would appear to be designed as much or more for service to the hospital rather than for broadly based training of the neophyte practitioner. Many medical schools have indicated an awareness of the problem, and some have introduced specific but limited programs into their curriculums. There is no implied criticism of the teaching experiments in family practice which are being offered students in a few schools and which include assignment of a family to a student for the four years of his medical school training, preceptorships in which the student spends all of a specified time during the curricular year with a specially selected general practitioner, and intermittent assignments in which the students make home visits with members of the teaching staff and/or visiting nurses. This is not the place to attempt an appraisal of the teaching methods now being tried, but it would seem that there is a real need for further experimentation in teaching techniques which might prove to be even more effective.

Integration between the curriculum of the medical school and the internship and residency program should be attempted in a few selected institutions which would be willing to give such a program an adequate test for a sufficient number of years and would provide adequate instructional supervision. There are a number of plans which might be tried. Specifically it would seem that the following are features which might be given more emphasis:

(1) Better correlation of preclinical and clinical teaching throughout the four years of medical school and the several years of hospital training.

(2) A broadly based, intradepartmental, introductory period to clinical medicine in which health and disease, the normal and the abnormal, are presented on a general basis. Such a plan would necessitate a certain amount of de-departmentalization initially in the clinical branches, with departmental instruction as such being limited principally to the clinical clerkship phase of teaching.

(3) Abolishment of the internship in a few centers with transfer of the usual intern responsibilities to the members of the fourth-year class of the medical school. Such a plan should result in increased clinical experiences for both third- and fourth-year students.

(4) A three-year post-medical school training program in the hospital for the family practitioner to be. Such a program might consist of one year of

internal medicine, one year of pediatrics, six months of obstetrics, and six months of minor surgery and surgical specialties. A portion of the surgical training period could be spent to advantage in an active admitting ward of a hospital. There are, of course, a great number of variations of such a plan which might be tried. Throughout all of these years, irrespective of the arbitrary length of training in the various branches of medicine, there should be a continuous program for psychiatric guidance of the resident physician for his management of patients in all of his services. It would also seem essential to such a plan that family practitioners should be on the teaching staff, that a substantial amount of time would be spent in the outpatient department of each service, and that home visits, both supervised and unsupervised, should be made.

(5) Postgraduate training through regular and frequent attendance of conferences in a medical center or annual refresher type of conferences are essential if the family practitioner is to keep abreast of current knowledge and practices. Medical schools must come to recognize that their responsibility to the physician does not end with his graduation.

Physicians adequately trained for so-called family practice should be able to provide a large proportion of the medical services required by the family including those for psychologic and minor psychiatric disturbances and particularly those in the category of family counseling. The preparation of medical students for family practice will and should decrease relatively the number of physicians who seek training in the various specialties of medicine and surgery and might thus serve to counterbalance the current tendency to overspecialization. The family practitioner will, in particular, compete with the internist, the pediatrician, and perhaps with the obstetrician. But there would seem to be more to be gained than lost by such an arrangement. The pediatrician should not resist it, rather he should welcome it as a means of providing better pediatric care for a greater number of children. Certainly his responsibilities will be increased; he will have to keep abreast of medical progress if he is to be the leader in the field. He must set the pace in everyday practice and provide the mark for which the family practitioner strives, and, if he is to be competent as a consultant, his stature, pediatrically-wise, must be at a higher level than that of the family practitioner.

THE PLACE OF THE HOSPITAL IN MEDICAL CARE FOR CHILDREN

The need for hospital beds for children has decreased during recent years and will probably continue to do so. This decreased need has been the result (1) of the marked improvement in the health status of children stemming from better socioeconomic and hygienic conditions as witnessed by fewer instances of severe diarrheal diseases, from preventive control of some of the acute contagious diseases, and from the effectiveness of antimicrobial agents in many otherwise severe diseases affecting children, and (2) from marked shortening of the individual child's stay in the hospital. There also is a decreased need for beds for some of the chronic illnesses. This decrease has been observed in orthopedic hospitals, heart hospitals, and

general convalescent homes. By contrast, there continues to be a need for institutional beds, which has never been adequately met, for mentally defective children, for those with psychiatric illnesses, and for those with severe crippling physical handicaps who could profit from long-term institutional care.

The generalization that the number of pediatric beds needed in a given community is in inverse ratio to the socioeconomic level of its members and the ability of its medical practitioners will probably stand up. If it is true, it indicates another reason for objective planning for the future to see that health funds are appropriately invested.

Community planning for hospital facilities is long overdue. Too frequently the reason for a new hospital or for expansion of an existing one is based principally upon factors other than community need or of integration with existing facilities. Much could be gained if personal and group interests, as, for example, those manifested by churches, racial groups, fraternal orders, segments of a large community, medical schools and even the city hospitals, themselves, could be submerged to over-all planning on a continuing basis. Nor are physicians as individuals and as groups without blame. It may well be that the larger share of it belongs to us. Certainly, if more effective and objective planning for hospital services is to be had, leadership or at least a high degree of cooperation will have to come from the medical profession. So that there may be no misunderstanding in respect to my thinking about community planning for hospital services, there is no intent to imply that hospitals should not have administrative autonomy, but simply that their lines of communication with other hospitals would be of an order to prevent overexpansion in regard to size or to services which were already available in sufficient quantity. There is an obvious need in all geographic areas of sufficient population for one or more essentially complete medical centers and for a larger number of less highly organized hospitals, which can provide medical and surgical services for the majority of ills and which, when necessary, can refer patients with the more complex diagnostic and therapeutic problems to the medical center. Such an arrangement can and should be in effect for all urban areas and the adjacent rural communities; it should include all hospitals, city, county, state, sectarian and nonsectarian, if it is to be economically and professionally effective.

A strong case can be made for the development and support of a few highly developed medical centers for children to be located in the larger cities and to be associated, if possible, with m e d i c a l centers of medical schools. This point of view was overwhelmingly supported (over 90 per cent) by the membership of the Philadelphia Pediatric Society through a questionnaire distributed by mail in 1946. It is not implied that community hospitals should not retain a few beds for children who require hospitalization for the more c o m m o n medical and surgical conditions. It is suggested, however, that medical and surgical conditions requiring more complex diagnostic and therapeutic facilities often can be more effectively and more economically managed in the medical center type of unit. The

marked improvement in transportation facilities has been an important factor in making the centrally located medical center practical. Patients can now be brought relatively long distances in comparatively short periods of time and usually without detriment to the pediatric patient.

The development of medical centers has, in the main, taken two directions. Each plan includes geographically centered complete facilities for the wide variety of diagnostic and therapeutic problems of pediatric medicine of acute and chronic natures. Both have stressed the importance and the need for integration and cooperation with other child-caring agencies within their area of influence. The difference exists in the nature of the arrangements with other agencies within the community: one proposes a closely unified, contractural relationship; the other a working understanding with other agencies within the community without contractural agreements.

Highly trained personnel both in general pediatrics and in the subspecialties together with appropriate equipment for their use constitute the basis for the medical center. Such personnel, in a pediatric institution which is designed to serve the community for all pediatric patients irrespective of their ability to pay, should be largely or wholly supported by salaries. Such an arrangement is essential if the cost to the individual patient is not to be prohibitive, if services can be available to all irrespective of economic status, and if the physician is to have time for teaching and research. Medical centers thus become expensive if measured by the cost of service per patient. If they are to be considered an essential in present-day medical practice, more adequate means for their financial support must be found.

A final word concerning the pediatric hospital and its relation to the practicing physician. It is of paramount importance that layman and physician alike recognize the relative place of the physician and the hospital in medical care for children. The surgeon, the obstetrician, and certain other specialists have most of their medical activities centered in the hospital. This situation does not hold in pediatrics. The practitioner through services rendered in his office or perhaps preferably in the child's home constitutes the basic and most important aspect of pediatric care. The hospital plays a secondary but essential role for the child's physician by providing:

(1) physical facilities for housing his patient when necessary and equipment which it would not be economical for him to own,

(2) specialized diagnostic and therapeutic services by physicians trained in the subspecialties of pediatrics,

(3) stimulation to his continued growth in pediatric medicine through the quality of care rendered his patient, through regularly scheduled medical conferences, and through refresher courses,

(4) training for the pediatricians of tomorrow who can serve him as assistants and/or eventually constitute his replacement,

(5) clinical investigation which may provide him with more effective methods for his care of patients.

THE PEDIATRICIAN'S RESPONSIBILITY TO THE COMMUNITY

In large measure, the pediatrician discharges this responsibility when he provides competent pediatric care for his child patient—not simply by the management of an incidental illness, but by long-term care, which includes all that is implied in preventive pediatrics and child guidance. It is in his repeated contacts with child and parents that he has perhaps the greatest opportunity for lay education in health matters available to anyone. That he has had some measure of success is attested by the respect generally accorded the pediatrician in the public health field. That he could accomplish much more than he does will be generally accepted.

There is not space here to go into detail of the various other responsibilities which the pediatrician has to the community. In addition to the general ones which all citizens should accept, the pediatrician should contribute to one phase or another of the public activities for children. Although his interests may naturally direct him into the health field, his contributions may be in other phases such as in education, recreation, prevention of delinquency, and the like. The important point is that he find a niche into which he fits and has the sense of making an effective contribution. The contribution need not be spectacular; it is usually preferable that it should not be. Not everyone can be a leader and he who serves most may consistently be in the ranks.

Medically, the pediatrician has a responsibility to participate in hospital and clinic services for the underprivileged, and, if he has the ability and the opportunity, in the teaching of medical students, interns, medical residents, and nurses.

Above all he should continually lend his influences to secure improved facilities for children within the community—educational, recreational, and medical. Most communities have a constant need for objective guidance in planning and an equally constant one for the fulfillment of these plans—even in the child health field. In these respects he can serve as a guide on the one hand, as a prodder on the other.

FINANCIAL SUPPORT FOR CHILD HEALTH FUNCTIONS

Most heads of pediatric departments and medical directors of children's hospitals or of pediatric divisions of general hospitals would give their eye teeth if their units could be self-supporting. But the eye teeth seem quite secure. Perhaps one advantage in what is truly a serious situation is the possibility that the raising of funds for health purposes from the members of the community provides opportunities for lay education and for development of an increasing sense of responsibility for financial support of local services. To date, we have not done a very good job, whereas national funds which take money out of the community have shown an increasing efficiency.

The financial phase of the pediatric problem is a large one and cannot be dealt with here in a comprehensive manner. I would simply like to highlight certain aspects, and especially those in which all of us have an opportunity to be effective, namely (1) local public health services for children, (2) financial support of pediatric hospi-

tals (3) special services for the handicapped child, (4) mental health units, and (5) teaching and research activities. In limiting ourselves to these aspects, we must be mindful that there are other needs for children which are of equal or even greater importance. These include improvement of socioeconomic situations through provision of better housing and family counseling and, without question, better educational, recreational, and vocational facilities.

Local public health services for children as well as for adults should be integrated with private facilities, and should not compete with them. The public health department should make use of available private services and assist in their expansion when such a course would appear to be more effective and more economical.

The *financial support of hospitals*, including pediatric ones, now comes in large measure from prepaid insurance plans such as that of Blue Cross. Physicians should not only encourage their patients to have such coverage, but they *must* take a large share of responsibility for the management of such funds through their selection of patients for hospitalization, for appropriate ordering of laboratory work, x-rays, and the like, and for avoidance of keeping the patient in the hospital for an unnecessarily long time. Abuses of Blue Cross by physician and layman can only make its cost to the subscriber unnecessarily high. One of the real needs of the moment is the extension of Blue Cross coverage for diagnostic services for both hospitalized and nonhospitalized patients. The administration for such services, however, seems fraught with many difficulties and could be possible only with meticulous selection of patients by the physician so as to avoid the many possible abuses. Other financial support for the hospital comes from direct payments by patients, grants for special services, income from endowment, annual direct gifts to the operative fund and, in Pennsylvania, per diem payments from the state to nonsectarian hospitals for indigent patients.

The great interest in the *handicapped child* which has been generated in recent years among laymen and by laymen has resulted in increased monies for certain types of handicaps. As might be expected under such circumstances, there is uneven distribution of the monies collected and heavy collection and administrative costs so that too low a proportion of the funds collected goes for the intended functions: direct aid to the patient, training of professional personnel, and research. No issue is taken with the conclusion that need for more effective services for handicapped children is overdue. The intent here is simply to speak for collection methods which are more objective and carry with them a more realistic explanation for the donor, for broader coverage of medical needs than a single disease, for lower administrative costs, and for greater emphasis on local supervision. This problem will be referred to again, but here let me emphasize that funds contributed for health functions come from your patients, your neighbors, your friends. Much of such giving is emotionally conceived. This cannot be completely eradicated and should not be. But if we are to have more adequate health services, it will

be due in large measure to the demand of an enlightened public who have come to know what constitutes good medical practice. The physician can make a significant contribution by helping the layman to understand the relative needs in the health field and by encouraging him to insist on effective management of such funds.

The need for funds for *mental health services* for children has been increasing rapidly in recent years. The demands for such services now far exceed the facilities for supplying them. I think most of us would agree that more funds should be directed into this field. One qualification which seems appropriate is that, owing to the relative newness of this field, financial support should also be available for investigative studies which appear to be adequately conceived and for whose conduct appropriate personnel are available. Another feature which seems important is the inclusion in the postmedical school pediatric training program of continuous psychiatric training—geared to make the physician for children more effective in the management and guidance of all of his child patients and in screening out at an early age those children who should be referred for psychiatric therapy. Prevention of behavior and psychiatric difficulties should be the principal long-range goal in the field of mental illness.

Adequate funds for the *departments of pediatrics* in the various medical schools must be made available if the foregoing suggestions are to have a chance of being put into operation. From where will "adequate funds" come? Departmental funds are primarily for salaries for the medical personnel who teach, carry out research, and provide specialized diagnostic and therapeutic services.

No attempt will be made here to define the minimum number of teaching personnel essential for a given department. I would like to emphasize, however, that there should be assurance of continuity of financial support for the key positions within the department. Certainly support for them should not be dependent upon annual grants-in-aid from outside sources.

Ideally, the bulk of departmental funds should be available on a continuing basis from the medical school. At the moment this situation does not exist in many institutions. Either the schools or the departments will have to find additional sources of continuing funds if a solution to this problem is to be found. At the present time, annual giving for teaching and research funds (medical school and departmental) would appear to be the best, but not the sole, source of additional funds. In this respect physicians have a great responsibility. Not only to make such contributions themselves, but to recognize the opportunity for lay education among friends and patients in regard to the bases on which they determine the distribution of their annual contributions.

Too large a proportion of funds for special medical services and for *medical research* are available only on short-time grants and with limitations which preclude development of departmental activities on as objective a basis as could be desired. Such funds are distributed through a variety of organizations, such as divisions of the Federal government, some state departments, commercial organizations,

private foundations, and national organizations developed for combating a particular disease. It would be quite unrealistic and unfair to leave the impression that such funds do not serve and are not serving a useful function. On the other hand, it is essential that careful and judicious consideration be given to their relative place in the medical field and to the adequacy of their management.

The principal functions of such funds are (1) to assist in the conduct of a particular research problem (project research), (2) to initiate special medical services often with the supposition that continuation, if justified, will be with funds from other sources, and (3) for training personnel in research and teaching.

The dangers which are inherent in the administration of such funds are several. There are the evils of so-called project research: (1) that the problem must be designed to satisfy the controlling person or board or must be related to the product of a commercial firm; (2) that the researcher must spend too much time in the preparation of protocols or in other endeavors related to securing the grant; (3) that the young man starting his career in academic medicine comes to think of research in terms of grants and develops his political acumen out of proportion to his investigative ability; (4) that investigators of proved ability are relegated largely to administrative capacities with much of their time being taken up in the securing of grants and in their management. There are many angles to this aspect. One observer has stated that, if the present situation continues with such a large proportion of academic funds available only on project bases, we can expect to see a marked shift in the requirements for departmental heads from academic to political abilities. It is not meant to imply that the situation is out of control, but it does seem essential that we recognize the existing dangers and the need for real leadership on a highly objective basis by medical persons and especially by those in administrative positions.

The layman is concerned principally with "funds for diseases." Most of these have been started by small groups of persons who find a particular reason for being interested in a particular disease, because a member of the family or a friend was afflicted. There is not much to criticize in such activities when they remain on a limited local basis. It would be preferable to be sure that such persons would become interested in health problems, community and academic, on a local basis. But experience has shown that such groups do not remain local. It is much simpler to appeal for funds for a specific disease than for general health needs or for nondesignated teaching and research funds. Within recent years and even months new "funds for disease" have emerged—and these for relatively uncommon afflictions. Where the trail will end is not predictable, but one can hope that the absurdity soon becomes more widely appreciated.

When the "fund for disease" becomes organized on a national basis, professional fund raisers come into the picture and what was a small local society is now big business. If large amounts of money are raised—and they are—they must be spent. The

dangers are obvious and known to all without elaboration here. The nature of publicity is often designed to make the layman believe that money per se will unravel the unanswered problems of the moment. The importance of training and developing promising young men and women for academic careers is not stressed. To collect increasing amounts of money in each succeeding annual campaign, the contributor must be shown that something is being done—and to be effective it must be dramatic. The costs of collection, of administration and of so-called "education of the public" are disproportionately high.

It has been said that these national funds do not compete with local organizations. This is not so. Many laymen think they have discharged their obligations to health needs when they have contributed to several of the "disease funds."

There are justifications for national funds and for grants-in-aid for research. The thought here is simply that there be established a reasonable balance. At the moment, the great need is to bring the layman back to a realization that he must support *local* health functions on a more adequate basis than he is now doing. It is not to be inferred that the writer does not recognize the existence of the same dangers in locally controlled funds as in nationally directed ones. There are the same needs for vision, objectivity, and honesty in both situations. But when funds are collected and expended locally, there should be lower costs of collection and administration and the layman has the opportunity to know more about the distribution and use of the funds so that he has a greater sense of participation.

Irrespective of how monies for health purposes are collected the responsibilities resting on those who must administer them is great. Except as this responsibility is discharged in such a way as to broaden the scope and sense of understanding of the layman, success has not been attained.

The child's physician—be he pediatrician or family practitioner—comes to recognize that his ultimate success is measured in the adequacy of the growth and development of his patient—physical, mental, and social. Collectively his patients of today will determine the pattern of living tomorrow.

If it is agreed that medical practice and training can be and need to be improved, then the problem is defined in general. Specific delineations of the various aspects are another matter. There is an obvious need for realistic and objective appraisal of the present situation to the end that the various aspects of the over-all problem come to be clearly understood.

In the final analysis the ultimate goal of medical practice is to eliminate the need for itself. Such a concept by implication reflects the most challenging definition of a profession: a group of persons skilled in a particular service to mankind who are constantly striving to eradicate the need for themselves. The pediatrician or the physician in most other phases of medicine need not fear that his profession is in danger of eradication in the foreseeable future.

Psychologic Aspects of Pediatrics

THE PSYCHOLOGIC DEVELOPMENT OF A GROUP OF CHILDREN BROUGHT UP IN A HOSPITAL TYPE RESIDENTIAL NURSERY

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THE care of young children in institutions is being widely discussed. Bowlby[3] reviewed this subject and cited numerous authorities, all of whom agree that life in an institution is seriously detrimental to the development of the very young child. Their conclusions can be summarized as follows:

1. Institution children show a statistically significant retardation in psychologic development as compared with control groups selected from the same social background.[10-12, 18, 20]

2. Quantitatively this retardation varies with the psychologic organization of the institution: degree of isolation of the children, number of personnel taking care of them, emotional attitude of these persons.[18]

3. This retardation varies also with the length of the stay in the institution.[18, 21, 22]

4. The various aspects of psychologic development are not equally affected; neuromuscular development is the least affected, language the most, and social adjustment somewhere between the two.[5-8, 11, 12]

Children placed in the usual type of residential nursery, where the staff can give only the simplest hygienic care, show a typical behavior defined by Bakwin[1, 2] (quoted by Bowlby) as "listlessness, emaciation and pallor, relative immobility, quietness, unresponsiveness to stimuli, indifferent appetite, failure to gain weight, . . . poor sleep, an appearance of unhappiness, proneness to febrile episodes, absence of sucking habits."

The authors attribute these phenomena primarily to the child's lack of regular contact with one particular adult, the mother or a mother-substitute, who shows love and interest toward the individual child. A further cause is said to be the absence of sensorial and social stimuli which are necessary to sound psychologic development.

Bowlby concludes his review by expressing the wish that all residential nurseries might be closed. Where necessary, he would place children in foster homes.

It is not our intent to question his conclusions. It seems worth while, nevertheless, to report the results obtained with children hospitalized in a nursery in which their psychologic development is given special thought and attention. The number of children we have been able to study does not, unfortunately, provide a basis for significant statistics. This study can have value only as suggesting a possible line of investigation.

THE INSTITUTION

La Clinique pour Nourissons, founded by Edouard Martin, in Pinchat, near Geneva, Switzerland, cares for twenty to twenty-five babies from

Address: 22 Rue de Candolle.

birth to 18 months, and occasionally older. Some children spend a short time there for medical or family reasons, or to solve some problem in the rearing of the child. Others stay long but cannot be studied for the purpose of this investigation because of individual peculiarities. Still others are there for reasons only of family or social circumstances, requiring a lengthy stay. The latter are the ones studied here.

Rooms.—Each of the four age groups has a bright room, divided by a glazed partition. Except in the youngest age group, two or three children are placed in each of these cubicles, since the age groups average four to six children.

Nutrition.—During the first three months most of the children are fed on demand. Thereafter they have four meals a day, with progressive introduction of fruit, vegetables, and cereals. Weaning from the bottle is early but adjusted to the development of the individual child.

Living Space.—At six months, the children are placed in a play pen once or twice a day for a period of time which increases with age; according to the season, they are in their room, on a terrace, or in the garden. As they learn to walk, they play more and more outside the pen, and are taken to other rooms in the building: the dining room, where the oldest take certain meals at the nurses' table, the kitchen, the office, etc. The staff aims, by a flexible routine and by frequent personal contacts, to make the life of the older children as nearly as possible like the life of children in a family.

Toys.—The children always have toys in their beds or in their play pens: rattles, balls, animals, dolls, blocks or other construction toys. The oldest group have a sandbox in the garden.

Toilet Training.—As soon as a child can sit up alone, he is placed on the toilet seat at regular hours. No pressure is placed on the child.

Staff.—The home has three registered nurses: One head nurse, one in charge of the premature and newborn babies, and one in charge of the formulas and bottles. The routine care of the children is in the hands of eight to ten student nurses. They are assigned by turns to each group of children for a period of two months, during which time they are responsible for the children, under the supervision of the permanent staff of registered nurses. Their attitude toward the babies in their daily contacts obviously varies with their characters. Their youth and the novelty of the techniques which they must learn create some difficulties in the establishment of easy contacts. However, their theoretical training includes courses in infant psychology, and their attention is constantly drawn to the importance of psychologic problems.

Relations With Parents.—The institution does not have stated visiting hours. In order to make as easy and as natural as possible their contacts with the children, parents are free to come at any time. Their professions and their places of residence prevent them in many cases from taking advantage of this freedom. The psychologic development of the child is thus based on his relations with the institution's staff.

The Children.—By administering Gesell's test, we determined the level of development of fourteen children,

five boys and nine girls, including one pair of twins. Twelve of them had been in the home since birth; the other two had been admitted at the ages of 12 and 14 weeks, respectively.

The Reasons for Admission.—The reasons for admission were: four cases, illegitimacy; two cases, the mother's profession; three cases, tuberculous mother; two cases, premature birth (birth at 6½ and 7 months); three cases, Iranian children sent to Switzerland for climatic reasons.

The family financial situation is, in most cases, comfortable. Only four children came from poorer class families: working men and petty clerks. Besides the three Iranian children, there were three French children, one Italian, and seven Swiss.

Physical Development.—In most cases physical development is normal; weight curves are excellent. Nine children were full-term babies, including one born by cesarean section. The other five, including the twins, were premature by four to ten weeks. Two of these had certain difficulties during the early weeks (cyanosis, skin hemorrhages, pretoxic stages), but developed well after those first weeks. Only one child, the male twin, is delicate, with a serious toxic condition at three weeks, frequent fevers and catarrhs and marked reactions to inoculations. The other children are in normal good health.

Psychologic Development.—The average age at the time of testing was 12 months, which corresponds for twelve of them to the average length of stay in the institution. The other two children, who had come to the institution later, had been there six and eight months, respectively.

The distribution by age was as follows:

Age in months	4	5	6	7	8	9	10	11	12	15	23	30
Number of children	1	2	2	1	2	1	1	1	1	2	1	

The distribution by developmental quotient (DQ) was as follows:

DQ	80	85	90	95	100	105	110	115
Number of children	2	3	4	3		1	1	

The median of the DQ's is 95. Considering 100 as normal, these children show a slight retardation. However, of the two children with the lowest DQ, one is the male twin, in delicate health, often in bed in isolation. The other is an Iranian child, always smiling, but exceptionally passive; he showed the same retardation in two tests administered three months apart.

Even though the psychologic development of these children is not quite up to the norms of children brought up in a family, it can be considered satisfactory.

Changes in DQ According to Length of Stay in the Institution.—Eight children were examined twice, the average age being 8 months at the first test, and 14 months at the second. The statistics given above include, for these eight children, the results of the second test.

The distribution of the DQ's on the two tests was as follows:

DQ	75	80	85	90	95	100	105	110
First test	1	1		1			3	2
Second test		1		2	2	2		1

Average on first test: 97.5
Average on second test: 95

The second test showed a tendency toward uniformity, concentrating the individual DQ's nearer the average, and also a slight lowering of the aver-

age. Examination of the eight individual cases showed: two cases, increase in DQ (average increase 17.5); five cases, decrease in DQ (average decrease 11); one case, unchanged.

To determine more accurately the development of each child, monthly tests should be administered. Slight fluctuations in DQ's are normal in view of the numerous and often imponderable factors which influence the test results.

The significant element in the statistics given above is the absence of any marked lowering of the DQ, which, according to the authors quoted earlier, should characterize a prolonged period of hospitalization.

Differential Development of Gesell's Four Aspects of Development in the Infant.—Several authors emphasize the fact that the different aspects of psychomotor development are not equally affected by the retardation caused by hospitalization. According to them, language and social adjustment are more affected than the motor responses. Our own results agree in this respect with their findings. The average for the four aspects of development is as follows:

Motricity	101
Adaptivity	97
Sociability	90
Language	89

A more detailed study of these fourteen cases provided the data shown in Table I.

TABLE I

	NUMBER OF CHILDREN SHOWING		
	RETARDATION	NORMAL DEVELOPMENT	ADVANCE
Motricity	6	5	3
Adaptivity	7	5	2
Sociability	11	2	1
Language	10	2	2

In the field of sociability, it is especially behavior at meals and control of the bladder and bowels that show a retarded development.

General Behavior and Reactions to the Test.—On the whole, the children are active and gay. They greet the members of the staff with signs of joy. They give the impression of being happy, outgoing children.

Their reaction to the test situation was usually good, provided the person administering the test put on the familiar white blouse. The tests were administered in the child's usual surroundings, often in the presence of members of the staff.

Certain children could not be tested during a period of excessive timidity toward strangers. Two children could not be tested at 15 months, although they had been easily tested at 10 and 11 months, respectively. One of the twins, untestable at 19 months, was perfectly amenable four months later.

Development After Leaving the Nursery.—At the time of writing, ten of these children have been away from the nursery for one or two years. Their development appears satisfactory. In no case do the parents complain of any particular difficulties in bringing up the children. We have, unfortunately, not been able to see them again, as most of them live abroad.

Only the twins could be retested after two and one-half months of family life; the results follow:

Test at nursery at 23 months	♀ DQ 100	♂ DQ 80
Test after two and one-half months of family life, at 27 months	♀ DQ 95	♂ DQ 90

The boy has made marked progress, but the girl appears to have slipped

backward. However, the nurse who supplied certain complementary information at the time of the first test seemed to have overestimated the linguistic development of the girl, who was then acquiring her simplest vocabulary. It is also true that minor fluctuations are always possible.

The children have adjusted easily to family life. Daytime dryness was acquired within a month. The girl's vocabulary has increased rapidly, while the boy still speaks very little and, in general, appears more passive. With their mother's helpful presence, they were willing subjects throughout the test. Their behavior at play is typical for well-developed 2-year-old children.

Possible Improvement in DQ During the Stay in the Residential Nursery.—During our study of changes in DQ as shown by two examinations six months apart, we had found two cases of marked improvement in DQ. One other case, not included in the preceding group, is worth mentioning. An illegitimate child, son of a nurse, had been placed in another institution in the city. Noticing that her child did not develop normally, the mother brought it to the nursery at 7 months. Tested three days after his arrival, he showed a DQ of 55. His appearance and behavior were those which are commonly described in children subjected to long hospitalization: listlessness, pallor, unresponsiveness to sensorial or social stimuli, frequent crying. Below are given the changes in DQ of this child during his stay in the nursery:

7 months (on arrival)	55
9½ months	65
11 months	60
14½ months	80

His behavior, too, begins to improve. He is still emotional, but the depressive attitude of his first months in the nursery is giving way to a more normal behavior pattern.

CONCLUSIONS

Although the number of cases examined is too small to permit drawing any firm conclusions, this study does appear to suggest certain possibilities.

The development of children placed in a residential nursery can apparently be very similar to that of children living in a family, provided the nursery is so organized as to care for the essential needs of the children. The average DQ of our subjects is indeed slightly below the normal, yet their whole behavior pattern gives the impression of a well-rounded development.

This appears particularly true for children less than 18 months old. Most children leave this nursery at an earlier age. The few who stay longer can be given special attention since there are never more than three or four of them at any one time.

The results have been achieved without undue expense for staff or equipment, but rather by constant attention to the psychologic development of the children.

So it seems that a new element is brought into the problem of the institutional care of children, at least during the early months. Placed in small, well-organized nurseries, they can profit by the constant medical supervision which is impossible in foster homes, while at the same time their psychologic development can be normal. This solution seems particu-

larly useful when the period of hospitalization can be limited to the earliest period of life.

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Juvenile Delinquency a Parental Responsibility

At a general Court held 13 Day of August 1651, if any person be found or it can be proved that by them any fruit be stolen or taken away unjustly off any mans land or ground, if the person or persons be under the age of sixteene yeares of age the parents of the said child or children shall severly correct them by whipping them and that to be done before some sufficient spectator, if the parent or parents of the said children doe refuse soe to doe, then the said person or persons are to be convicted before the magistrates, and the parents for their neglext of the children to undergoe such penalty as the magistrate shall lay upon them.

SOUTHHAMPTON (LONG ISLAND) TOWN RECORDS.

Comments on Current Literature

EPIDEMIOLOGY OF POLIOMYELITIS

AS A result of concerted efforts to learn more about the natural history of poliomyelitis, certain aspects of this perplexing problem have been elucidated. Yet there are many epidemiologic features which still remain obscure. A significant study pertaining to the epidemiology of poliomyelitis is reported in the April, 1955, issue of the *American Journal of Public Health*. This report, entitled "Serologic Epidemiology of Poliomyelitis," by Melnick, Paul, and Walton[1] presents the results of serologic studies carried out in three widely different types of community: isolated arctic communities, subtropical areas in the vicinity of Cairo, Egypt, and in the American city of Charleston, West Virginia, a community where existing sanitary conditions are remarkably varied. Basing their investigations on the recognized immunologic principle that specific antibodies appear in the serum as a part of the body's response to infection, whether caused by bacteria, rickettsiae, or viruses, the authors undertook antibody-titer surveys of the populations in these various communities with a view to ascertaining whether poliomyelitis was prevalent in the community, when infection with poliomyelitis viruses probably occurred last, and what portions of the population groups were affected most. Similar serologic studies have been carried out for yellow fever, and more recently for influenza.

The introductory portion of this report comprises a brief summary of what is known concerning antibodies and immunity to poliomyelitis: that antibody response to infection occurs regardless of the type of infection, whether inapparent, subclinical, or accompanied by serious illness; that two types of antibodies are recognized, the neutralizing and complement-fixing antibodies, etc. Neutralizing antibodies are long lasting, perhaps for the entire life span, whereas complement-fixing antibodies are short-lived, disappearing as a rule within a year or so after infection, or present at very low level. The presence of neutralizing antibodies is believed to be associated with a state of immunity against the disease.

The investigations by Melnick, Paul, and Walton were well planned, and the results analyzed carefully. Isolated Eskimo peoples are rarely attacked by polio. In one such Eskimo community, Barrow Village, serologic studies showed that neutralizing antibodies to Type II (Lansing) strain of poliomyelitis virus were present in high titer in persons of 20 years or older, but were almost entirely absent in those under this age. Antibodies against Type I (Brunhilde) were found in highest percentage in persons 30 years of age or more, and Type III (Leon) in those 40 years of age or more. The authors interpreted these findings to mean that in all probability antibodies against Types I and III viruses can persist for thirty to forty years in the absence of reinfection, since there has been no evidence to suggest that exposure to these two types of virus has occurred in this area within the past thirty years.

In contrast to these findings in the remote isolated Eskimo populations of northern Alaska, those obtained for the urban population of subtropical, crowded Cairo, Egypt, gave evidence

of widespread infection with polio viruses. While clinical poliomyelitis is unusual in the native adult in this area, there is good evidence that neutralizing antibodies to all three types of poliomyelitis virus are acquired at an early age.[2] Children are born with neutralizing antibodies which disappear gradually over the period of the first six months of life. Surveys reveal that after six months of age, antibody titers begin to rise again almost immediately, so that more than 50 per cent of the infants followed had antibodies for Type II before they were 2 years of age, and for all three types, 75 per cent or more of the children had neutralizing antibodies before they reached the age of 4 years. These neutralizing antibodies acquired in early childhood appear to be retained at high level throughout life. It is of interest that in these studies the complement-fixing antibodies, which are relatively short-lived, rose sharply in titer at the age of 1 year, remained fairly constant through the ages of 5 to 9 years, and then declined sharply. Sera from populations in French Morocco* are being investigated; to date the results are very similar to those obtained for the Cairo area.

In Charleston, West Virginia, where sanitary conditions vary considerably from one part of the community to another, the development of neutralizing antibodies was shown to be delayed, not reaching 80 per cent incidence before the age of 30 years. Complement-fixing antibody titers observed in this locality indicated that new infections or reinfections were spread over this thirty-year period. In the Charleston area two distinct regions were studied: in district one, where sanitary conditions were very poor, a rapid rise in antibody level occurred in the earlier years of life, after which a high level appeared to be maintained into adult life. In district two, comprising a population of middle or upper-middle class socioeconomic status, where better sanitary conditions obtained, antibody levels were shown to have a slower rise, attaining an incidence of 50 per cent only after the age of 15 years, and reaching high levels only at 40 years or over. This inverse relationship between antibody levels to poliomyelitis viruses and cleanliness has been observed in many instances where the physical environment was substandard. Distribution of paralytic cases of poliomyelitis in the Charleston area was also pertinent to this observation: in a group of 27 recognized cases, for example, occurring over a given summer period, only three were from the lower socioeconomic group, and the remainder, 17 paralytic and 7 nonparalytic cases, were from upper middle-class families. It was "evident that children in the poorer districts were not providing clinical cases at the same rate as those of middle-class status at ages beyond infancy."[1]

Such studies in serologic epidemiology should add considerably to our knowledge of the natural history of poliomyelitis, and improve our understanding of the endemiology of this virus infection. With the advent of active immunization against poliomyelitis, as the authors point out, serologic studies should be of considerable value in furnishing information as to the immunologic status of various communities, and of defined segments within a single community, and might furnish valuable information as to when and where vaccination programs should be carried out.

RUSSELL J. BLATTNER

*Studies by Paul and Horstmann.

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Correspondence

A LETTER FROM LONDON

Knowing the interest that retrolental fibroplasia has aroused, I would like to draw attention to the presidential address delivered by Dr. C. T. Potter in 1954, to the Section of Paediatrics of the Royal Society of Medicine. He discussed the problem of blind children, a matter of importance to all paediatricians, and one of which he himself has had very considerable experience.

An analysis of the diagnosis in cases of blindness interviewed at the Royal Institute for the Blind between October, 1951, and December, 1953, showed that of a total of 283 cases, no less than 151, that is, 53.3 per cent, were attributed to retrolental fibroplasia. The increase in incidence of this condition is well brought out by a consideration of the year of birth of 177 infants who had been afflicted with retrolental fibroplasia, and were seen at the Royal National Institute for the Blind or at the Sunshine Homes for Blind Babies between 1946 and 1951; 5 were born in 1946, 12 in 1947, 21 in 1948, 47 in 1949, 44 in 1950 and 48 in 1951. Retrolental fibroplasia is at the present time by far the commonest single cause of blindness in children in this country. The incidence of the condition in small immature infants is, of course, well known, and it is strikingly brought out by Potter, who states of these 177 cases the birth weight of as many as 165 lay between 2 pounds 2 ounces and 3 pounds 15 ounces. It is worth while mentioning that 85 of these were regarded as of normal intelligence, 45 as retarded, and 35 as mentally defective.

Turning to the general physical health of premature infants, Douglas and Mugford have published an interesting paper (Brit. M. J. 1: 748, 1953) comparing a national sample of 676 premature infants (birth weight 5½ pounds or less) with a carefully chosen group of controls. During the first two years of life the prematurely born children showed a higher incidence of hospital admissions, many of which were for bronchitis and pneumonia; both upper and lower respiratory infections were more common during these first two years, and this susceptibility was found even among those who were reared in an apparently favourable home environment. On an average, the premature children spent about three and one-half times as many days in hospital during the first years of their life as did the controls. After the age of 2, premature children in general appear to be as healthy as those who are not so handicapped.

Considerable feeling and public comment have been recently aroused in this country over what are termed in our press "horror comics." On October 21, 1954, in the House of Commons, four members of Parliament asked the Home Secretary questions on this subject, the gist of which was to draw attention to the type of publication which has for some time been causing apprehension. On October 30, the *British Medical Journal* devoted much space to the subject, and took the view that such publications by and large have a very harmful influence because of the scenes of horror, terror, and unbridled violence (some of which are regarded as frankly obscene) which they present.

As many of these publications appear to be imported from the United States, it is interesting to compare the views expressed over here with the editorial comment in the June, 1953, number of THE JOURNAL OF PEDIATRICS. From this it seems that the Editor felt that the children of today are no more likely to be harmed by "comics" than were the children of the '90's by the dime novel. He clearly did not feel that the "comics" were having a really bad influence on children in America. In this he was supported by the article of Dr. Ruth Bakwin in the May, 1953, number of THE JOURNAL OF PEDIATRICS. Dr. Bakwin felt that propaganda, simplified teaching, and presentation of social situations and historic incidents are all within the range of subject matter

for the "comics," and therefore she regarded them as having, among other things, a high potential value as an educational medium. These views expressed in your JOURNAL must command attention and respect, but we feel very differently about it, and as I cannot believe that the British child is so much more impressionable for evil than the American child, I am left wondering whether the type of publication being referred to is really the same in both cases, or whether things have altered for the worse in the last year or so.

The *British Medical Journal* opened an annotation on this matter in its issue of October 30, 1954, as follows: "Probably few medical men have seen what, by a strange abuse of language, are called 'comics,' and many believe that they are just exaggerated versions of the relatively innocent 'penny dreadful' of their youth. One look at them has been enough to convince the new Home Secretary, Mr. Lloyd George, that some action is necessary—action, it is hoped, that will be speedy and effective to prevent the sale of a foul kind of literature calculated to violate the immature mind." The general press adopted a similar tone, and the London *Times* devoted a leader to the subject. Action has now been taken, and on February 11, 1955, the Government introduced in Parliament a bill which proposed to make it an offense to print, publish, or sell certain "pictorial publications harmful to children and young persons." The maximum penalty would be four months' imprisonment or a fine of £100 or both. The Bill is called the Childrens and Young Persons (Harmful Publications) Bill, and it is aimed at suppressing the publication and importation of "comics" of the horror type. We must now wait to see what actually happens.

The editorial article "Is Breast Feeding Worth Salvaging?" in the October, 1954, number of THE JOURNAL OF PEDIATRICS is a most interesting one. As you specifically invite comments, may I say that it is quite clear that the same sort of difficulties and influences operate in regard to this matter in our two countries. Most of us here feel that it is highly desirable for a mother to breast-feed her infant, and that the majority can do so if they are prepared to take a little trouble, and if the difficulties that may arise are properly handled by someone *who is really interested* and who understands the problems involved. However, relatively few medical practitioners are familiar with the details of the subject (or care very much about it), and as it is easier and less bothersome to bottle-feed many infants, the line of least resistance is adopted. It is, unfortunately, not enough that the paediatrician should advocate breast feeding. For this to be successful it should, of course, commence with the obstetrician taking an interest and exerting his influence, and this should be reinforced by the maternity nurse and by all those who, in one way or another, are intimately concerned with the care and management of the mother and infant. I consider that breast feeding is worth salvaging, and that an effort should be made to do so.

I began this letter with some comments on blind children; may I end it by mentioning that, at the time I am writing, that remarkable woman, Miss Helen Keller, is visiting this country, and has had a meeting with Sir Winston Churchill. The story of her life is a great example of courage, perseverance, and concentrated effort. Her triumph over the dual disability of blindness and deafness contracted in infancy, and her subsequent life of service to others, is an inspiration to us all.

KENNETH H. TALLERMAN.

News and Notes

Dr. Howard Childs Carpenter of Philadelphia died April 7, 1955, after an illness of several years. Dr. Carpenter was medical director of the Children's Hospital in Philadelphia from 1913 to 1939, and professor of pediatrics in the Graduate School of Medicine of the University of Pennsylvania for many years. He was a former president of the Children's Bureau of Philadelphia and of the Children's Hospital Association of America. He was elected to the American Pediatric Society in 1911, and served as its secretary from 1917 to 1931 and president in 1932.

The **Pan American Sanitary Bureau**, Regional Office for the Americas of the World Health Organization, is planning to conduct a **Survey of Pediatric Education in Latin America,** beginning in July, 1955, similar to those which have been carried out in the United States, Canada, Europe, Australia, and New Zealand. The Latin American survey, which will cover twenty-one countries and approximately seventy-five schools, will take place in the summer and fall of 1955 and will be under the general direction of Dr. Myron E. Wegman, Chief of the Division of Education and Training of the Bureau, and formerly professor of pediatrics at Louisiana State University. Dr. James G. Hughes, professor of pediatrics at the University of Tennessee, will act as special consultant for this program and will be visiting a large number of the schools. Endorsement of the program has been given by the International Pediatric Association and the American Academy of Pediatrics, whose country chairmen and secretaries will be collaborating in the gathering of information.

The **Seventh Postgraduate Assembly in Endocrinology and Metabolism** sponsored jointly by the **Endocrine Society** and the **Indiana University School of Medicine** at the Indiana University Medical Center, Indianapolis, will be held Sept. 26 to Oct. 1, 1955. For further information concerning the program, write Post Graduate Office, Indiana University Medical Center, 1100 West Michigan St., Indianapolis 7, Ind. Registration is limited to 100.

The **American Academy of Pediatrics** will grant twelve or more fellowships for pediatric residents for a period of six months to one year. These fellowships have been created to enable young physicians in financial need to complete their pediatric training. The fellowships carry a stipend of $500 to $1,000, depending on the length of time required to complete training and the need. The fellowships have been made possible by a grant to the Academy from Mead Johnson & Company and will be granted as of July 1, 1956. *The deadline for receipt of applications will be March 1, 1956.* Those interested in applying may correspond with the American Academy of Pediatrics, 610 Church St., Evanston, Ill.

A **Fellowship in Pediatric Neurology** is now available in the **Children's Division of the Cook County Hospital** under the auspices of the Dr. Julian D. Levinson Research Foundation. Stipend: $5,000 per year. For further information, contact Dr. Abraham Levinson at Cook County Hospital, Chicago 12, Ill.

A three-day International Symposium on **Enzymes: Units of Biological Structure and Function,** sponsored by the **Henry Ford Hospital** and **The Edsel B. Ford Institute for Medical Research,** will be held in the auditorium of Henry Ford Hospital, Nov. 1, 2, and 3, 1955. Interrelationships between enzymology and other fields, notably genetics, physiology, biochemistry, and pharmacology, will constitute the general theme of the Symposium. The specific topics for the six sessions will be: Origin of Enzymes, Status of the Gene-Enzyme Re-

lationship, Enzymes and Cell Structure, Enzymatic Basis of Some Physiological Functions, Cellular Energy Sources, and Regulation of Enzyme Activity. More than thirty internationally known scientists have accepted invitations to participate. Interested persons may secure a copy of the Preliminary Announcement by writing to Dr. Clarence E. Rupe, Henry Ford Hospital, Detroit 2, Mich. Invitations will be sent to as many as can be accommodated.

The **New York Medical College-Flower and Fifth Avenue Hospitals** announces a postgraduate course in **Pediatric Allergy** under the direction of Dr. Bret Ratner, Nov. 2, 1955, to May 21, 1956, thirty sessions, on Wednesdays, 9 A.M. to 4 P.M. Applicants must be certified in pediatrics or have the requirements for certification. Enrollment limited. Apply: Office of the Dean, New York Medical College, Fifth Ave., at 106 St., New York 29, N. Y.

Book Reviews

The Diagnosis and Treatment of Convulsive Disorders in Children. Samuel Livingston, M.D., Springfield, Ill., Charles C Thomas, Publisher, 320 pages. Price $9.50.

Sections in pediatrics textbooks dealing with convulsive disorders in infancy and childhood are generally inadequate and often uncritical. The need for an authoritative book on the subject has been pressing for a number of years. An authoritative work on this subject should therefore be welcomed by those who are interested in neurological and epileptic disorders in the young.

The book is handsomely printed and the type face and setting make for easy reading. The author and subject indices are well prepared. The chapter on surgical treatment of epilepsy is a model of clarity and simplicity. Complete critical summary of the indications, techniques, and values of surgical approach of epilepsy, including the recent use of hemispherectomy, are presented.

Elsewhere in the book, many of the statements and viewpoints appear somewhat uncritical and often add little to the typical general textbook treatment. For example, the classification used follows the conventional textbook pattern, namely, by seizure types. Because "epilepsy" is a symptom of different disease entities, a classification on etiological basis would seem to be a more rational and useful scheme.

In the light of the careful work of Lennox, Gibbs, and others, it does not appear justifiable to differentiate "petit mal spell" from "minor motor seizures" by considering "simple staring" as a "petit mal spell" and the "akinetic" and "myoclonic spells" differently. The statement that akinetic spells occur almost entirely in patients with organic brain damage is at variance with our experience and most other workers in the field. All of these three seizure types occur in epileptics of idiopathic as well as organic origin. As to massive myoclonic seizures, they constitute a specific entity. Their clinical, electroencephalographic and prognostic characteristics are distinctly different from the above conditions. They properly belong to Gibbs' hypsarhythmia group.

One of the most interesting problems in epilepsy today is the psychomotor or temporal lobe seizure. Many practicing physicians are not familiar with this entity and tend to confuse these seizures with behavior disorder associated with cerebral dysrhythmia. The discussion in this book, it seems, furnishes little clarification and in at least one instance confuses the two entities. In the cases presented, the brief and limited histories and the lack of electroencephalograph illustrations leave much to be desired. In the only case (Case 17) where a sample of the electroencephalogram is shown, the reported findings of a normal waking record, and high voltage spike wave forms in all leads asleep are not generally considered consistent with psychomotor seizures. On the other hand, focal temporal abnormality,

which is characteristic of psychomotor epilepsy, is reported in only four out of the author's series of 209 cases.

In the chapter on medical treatment, the section on ketogenic diet is very instructive and should prove very helpful to the practicing physician. It should be stressed, however, that in the very young, extreme care should be exercised during the period of starvation as severe acidosis and coma may ensue with little warning. In our recent experience, Thorazine is very useful in alleviating nausea and vomiting of starvation. Although the author agrees that Tridione is the most effective drug for petit mal seizures, he does not use it because of its possible toxicity. In our hands and in the experience of many others, when proper precautions are followed, Tridione has been used with safety in a very large number of cases. The author's practice to start patients with petit mal epilepsy on Dilantin or phenobarbital, together with anti-petit mal medication, is based on the belief that patients with petit mal epilepsy are prone to develop major motor seizures. In our experience, this prophylactic measure has generally proved to be unnecessary, as a large number of patients with petit mal seizures never develop generalized motor seizures.

With regard to febrile convulsions, the author does not advise treatment unless there are "four episodes within a year." This criterion seems quite arbitrary and probably entails unwarranted risk in certain cases. We believe that there should not be set rules but that each individual case should be considered on its own merit.

A reference book of this nature and purpose needs to be concise, accurate, and critical. In these regards, the present volume does not appear to have succeeded in a number of instances. For example, the "pitressin hydration" test, which has been discredited and largely abandoned because of its nonspecificity, is reported as a diagnostically valid test for epilepsy on the authority of its originator; but no statement is given of the personal experience of the author which would support this contention, and the work of others who report contrary evidence is not cited.

Statements such as "sleep seizures are mostly major motor in type," "the electroencephalogram is almost always normal in patients with purely myoclonic epilepsy," and many others of similar nature, we believe, need more critical evaluation or at least statistical confirmation.

D. C.

Fractures in Children. Walter P. Blount, M.D., Baltimore, 1955, The Williams & Wilkins Co., 279 pages. Price $9.50.

Dr. Blount's monograph is based on the experience of the Fracture Service of the Milwaukee Children's Hospital over a period of more than twenty years. In an introductory chapter, the differences between the treatment and results of fractures in children and adults are discussed. This is followed by chapters describing the fractures and treatment occurring in different bones. The text is beautifully illustrated with over 300 illustrations. These not only point out what should be done but emphasize what should be avoided. While of particular interest and value to the orthopedist, the pediatrician will find much in it of interest.

Christopher's Minor Surgery. Edited by Alton Ochsner, M.D., and Michael E. DeBakey, M.D., Philadelphia, 1955, W. B. Saunders Co., 547 pages. Price $9.00.

The seventh edition of Christopher's *Minor Surgery* is edited by Ochsner and DeBakey with chapters contributed by about twenty surgeons of the Tulane and Baylor groups. It follows the usual discussion of surgery by systems. Chapters on anesthesia and surgical dressings are included. It is difficult to draw a distinction between major and minor surgery in some instances. The authors have included some subjects such as pilonidal sinus that may require surgery of a "major" character. The book will be of particular interest to the surgical resident.

Editor's Column

SOME REFLECTIONS ON THE SALK VACCINE

WITHOUT intending to minimize in any way the brilliant contributions which have culminated in the production of the Salk vaccine, it is necessary for the physician to keep clearly in mind that the last word has not been spoken. Unfortunately the use of such flamboyant inaccurate headings in the newspapers as "Polio Conquered" has led the vast majority of parents to believe that *finis* has been written to the polio problem. This is far from true.

Physicians were waiting for the Ann Arbor report on April 12, with two questions in mind: How good is it? and Is it safe? The answer given was that the vaccine was safe and the results favorable. The results, however, were far from showing that at its present stage of development the Salk vaccine is the final answer. The statistics gathered from the 1954 study were interpreted as allowing of the estimate that the vaccine was about 60 per cent effective against paralytic polio with Type I infection, and 70 to 80 per cent effective against paralysis with Types II and III infection. Unfortunately, the many large epidemics of paralytic poliomyelitis have been almost entirely due to the Type I virus. Only a few small epidemics have been reported as due to the Type III virus, and none to Type II. Salk's studies show that different batches of the present vaccine vary in their ability to provoke antibody response, and that the titer produced fell more rapidly with some than with others. He believes that with a constantly improving vaccine these differences can be eliminated, or, in other words, it is a technical matter rather than a fundamental problem. We sincerely hope he is right, but the value of the vaccine must be judged by the vaccine in current use.

The presentation of the report at Ann Arbor was followed by rush shipments of stored vaccine to all parts of the country. The clamor became so great that a hasty conference had to be called in Washington to consider its allocation. Then came a tragedy. It was found that children inoculated with the vaccine were coming down with paralytic poliomyelitis. Some of these cases developed in communities where it was not "polio season," and there was a shortened prodromal stage. It necessitated recalling all of one vaccine that had not already been used. The

California Board of Health prohibited the use of all Salk vaccine in that state until more information as to its safety was available. When the number of reported cases of paralytic poliomyelitis in vaccinated children reached a total of 50, the Public Health Service on May 7, reversing a stand taken only two days previously, recommended that the vaccination program be temporarily suspended until further checks could be made of the safety of the vaccine. This is the status as we go to press.

The news of the lack of safety of the vaccine was broadcast throughout the country. The parents of children who had been given vaccine were frantic, as the nation-wide excitement created by the publicity-craving Polio Foundation had led the public to believe that an absolutely safe vaccine had been developed. Had the vaccine been developed and introduced for general use in the customary way, slowly and with carefully controlled studies, the end result might have been the same, whatever it may eventually turn out to be. The public, however, would not have been plunged from a pinnacle of great expectations to the depths of fear and confusion in a space of less than a month. The blame will unjustly be placed on the medical profession, and not, in our opinion, where it chiefly belongs. All in all, it has been a tragic experience.

The Salk vaccine, moreover, does not put an end to the moot question of a live-virus vaccine versus a killed-virus vaccine. Salk[1] has ably presented his own and the views of those who support a killed-virus vaccine. However, there are a number of scientists who hold to the principle of an attenuated live-virus vaccine. Bodian[2] recently stated that "promising results" have been obtained in developing a live-virus vaccine in four laboratories and Sabin reported on its oral administration in a small group. Which is preferable is a matter that can only be determined and settled by the studies of the immunologists. It is not a question in which opinion is of the slightest value.

We have great admiration and respect for Dr. Salk. He is a brilliant and able scientist of whom American medicine is proud. The insistence he has placed on the Salk vaccine being the outgrowth of the work of others, as Landsteiner and Enders, who pioneered various steps which made the vaccine possible, does not detract from the importance of his own work, but adds to his stature and integrity as a scientist. All honor to him.

Granted that funds provided by the Polio Foundation aided the research, and made possible the mass experiment of 1954, our feeling toward the Foundation is distinctly critical over the way in which it submitted the report by Dr. Francis for public acclaim, and not for careful scientific scrutiny, study, and criticism. A Public Health official aptly described the distasteful proceedings, unparalled in scientific annals, as a "Soap Opera." Only time will give the Salk vaccine its proper place in medicine. While we sincerely hope it will be a high place, from the results appearing in the report it is today far from being the "solution

to the polio problem." To have created a public belief to this point by the unnecessary and unjustified methods of publicity used by the Foundation is cruel.

The harm has already been done and we recognize full well it cannot be undone. What makes us truly apprehensive is the fact that there are numerous other "fund for a disease" organizations. Seeing the financial success of the Polio Foundation publicity experts, what is to prevent others from adopting similar methods? There are other diseases far more common and far more dangerous in their crippling and death rates than polio, as, for example, rheumatic fever and cancer. Think what would happen if a similar publicity stunt were developed for a promising experimental cancer cure. The Polio Foundation has created a situation that, we feel, is of the greatest importance to the integrity and to the future of medicine. Many thinking physicians have been concerned over the methods used by and the mushroom growth of these ancillary medical groups. These fears are now shown to have been justified.

The reason why it has come about was clearly, although unconsciously, presented in one of the many newspaper stories that have flooded the press in recent weeks. Under a picture of Mr. O'Connor the caption read as follows: *"Basil O'Connor, President Roosevelt's one time law partner, who decided that laymen would run the National Foundation for Infantile Paralysis, with scientists, and medical experts in an advisory role."* What right, we ask, has a lay-controlled organization to decide and pass judgment upon technical medical matters, and utilize the research of medical scientists in a publicity stunt? It may be argued that the controlling body of most medical schools, research institutions, and hospitals consists largely of lay individuals. While this is true, it is the first time to our knowledge that a controlling board has ever made such use of scientific work, or directed how the scientific work should be made avaliable to other scientists and to the medical profession which has the ultimate responsibility for its use.

No one questions the integrity or competence of the many men of science who contributed to this study. On the other hand, there must be many with contrary opinions, with alternative methods, or even with conflicting interpretations of the field trial data, who should have been given the opportunity to be heard before its presentation ex cathedra to the public. These are the safeguards which have been used by medical scientists for many generations for determining the value of a proposed therapeutic procedure, with the purpose of protecting the public and maintaining the integrity of the medical profession.

If the measure of the success of publicity is quantity, the Foundation has made a world record. The vaccine has been "front page news" for a month, and the subject of innumerable magazine articles. The number of public health officials, physicians, and politicians who have been quoted on one aspect or another runs into the hundreds. We feel, however, the publicity has backfired. Newspapers whose editors were fulsome for the first two weeks are now critical of

the muddling and confusion that has developed. According to press reports, two congressional committees are about to investigate. The issue of government against private enterprise control has arisen. There will be repercussions for many years to come, and the happenings of these four weeks will be a nightmare that will haunt the dreams of scientists and public health officials for generations. It all would have been avoided had the evaluation and use of the vaccine been left to the medical profession to handle in the way it has handled other therapeutic advances as, for example, insulin.

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